VOLUME 58 • DECEMBER 1957 • NUMBER 6

OPHTHALMOLOGY

INDEX NUMBER

Circinate Retinopathy
William R. Houston and George N. Wise
Part I
Part II

The Scleral Buckling Procedures
C. L. Schepens, I. D. Okamura, and R. J. Brockhurst

Experience of Treating Retinal Venous Occlusion with Anticoagulant and Antisclerosis Therapy
Salme Vannas and Heta Orma

Experimental Studies of the Choroidal Vessels
Enrique Wudka and Irving H. Leopold

The Agar-Diffusion Technique in Studies of Immunity to Adenoviruses
Chie Tanaka

Eosinophilic Granuloma of the Orbit
M. S. Nirankari, Manmohan Singh, S. S. Manchanda, N. L. Chitkara, and M. C. Maudgal

Glaucoma, 1956-1957
Bernard Becker

News and Comment

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TABLE OF CONTENTS

VOLUME 58 DECEMBER 1957 NUMBER 6

ORIGINAL ARTICLES

PAGE

Circinate Retinopathy

William R. Houston, M.D., and George N. Wise, M.D., New York
Part I 777
Part II 783

The Scleral Buckling Procedures

C. L. Schepens, M.D.; I. D. Okamura, M.D., and R. J. Brockhurst, M.D., Boston 797

Experience of Treating Retinal Venous Occlusion with Anticoagulant and Antisclerosis Therapy

Salme Vannas, M.D., and Heta Orma, M.D., Helsinki, Finland 812

Experimental Studies of the Choroidal Vessels

Enrique Wudka, M.D., and Irving H. Leopold, M.D., Philadelphia 829

The Agar-Diffusion Technique in Studies of Immunity to Adenoviruses

Chie Tanaka, M.D., Bethesda, Md. 850

Eosinophilic Granuloma of the Orbit

M. S. Nirankari, F.R.C.S.E.; Manmohan Singh, D.P.H.; S. S. Manchanda, M.D.; N. L. Chitkara, M.D., and M. C. Maudgal, D.O.M.S., Amritsar, India 857

ANNUAL REVIEWS

Glaucoma, 1956-1957

Bernard Becker, M.D., St. Louis 862

REGULAR DEPARTMENTS

News and Comment 923

A. M. A.
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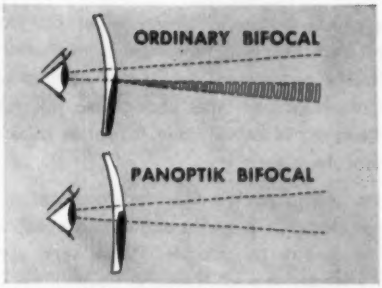

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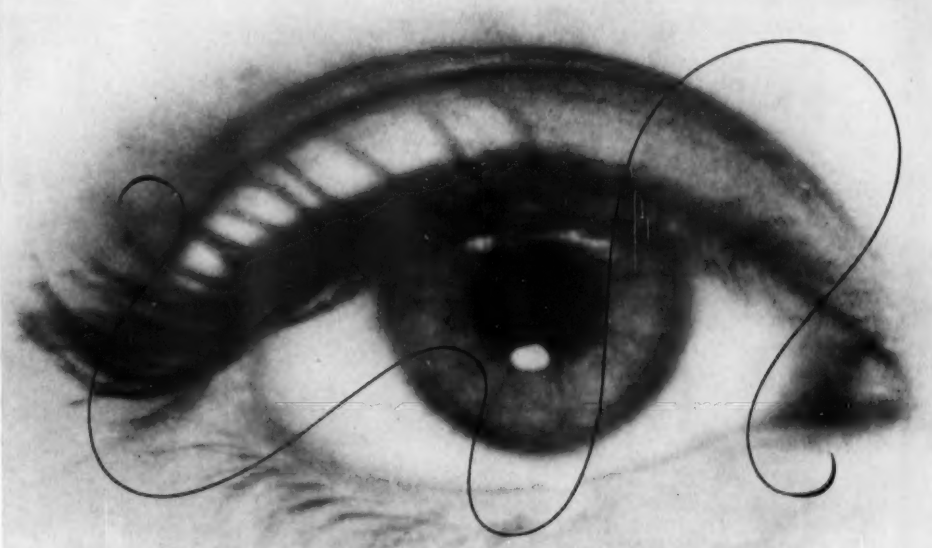

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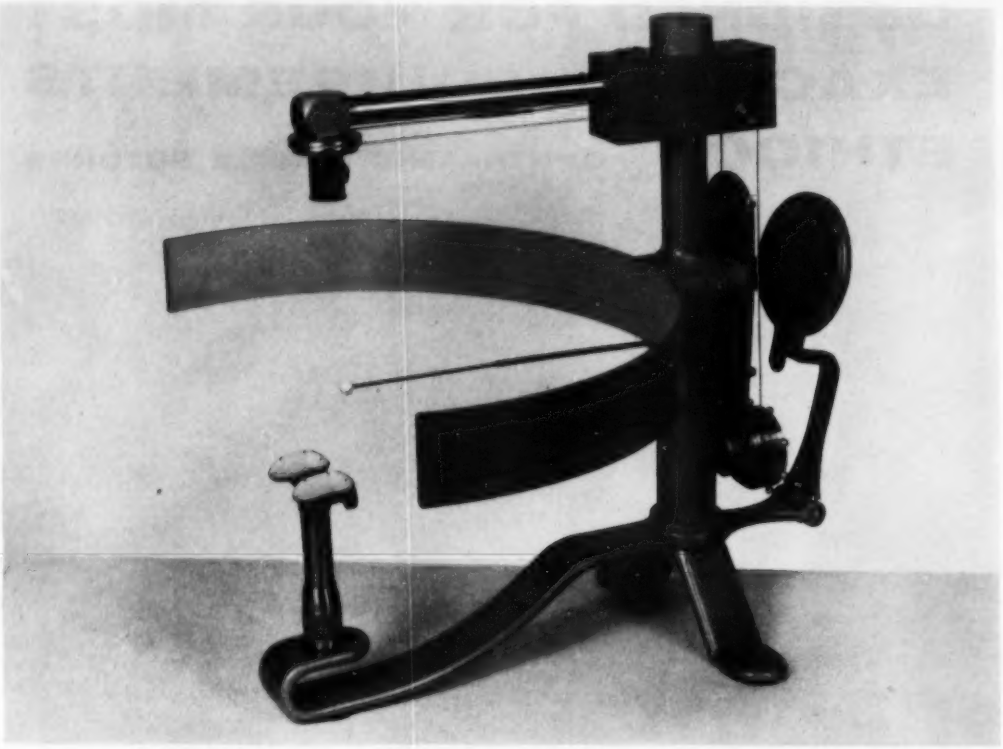

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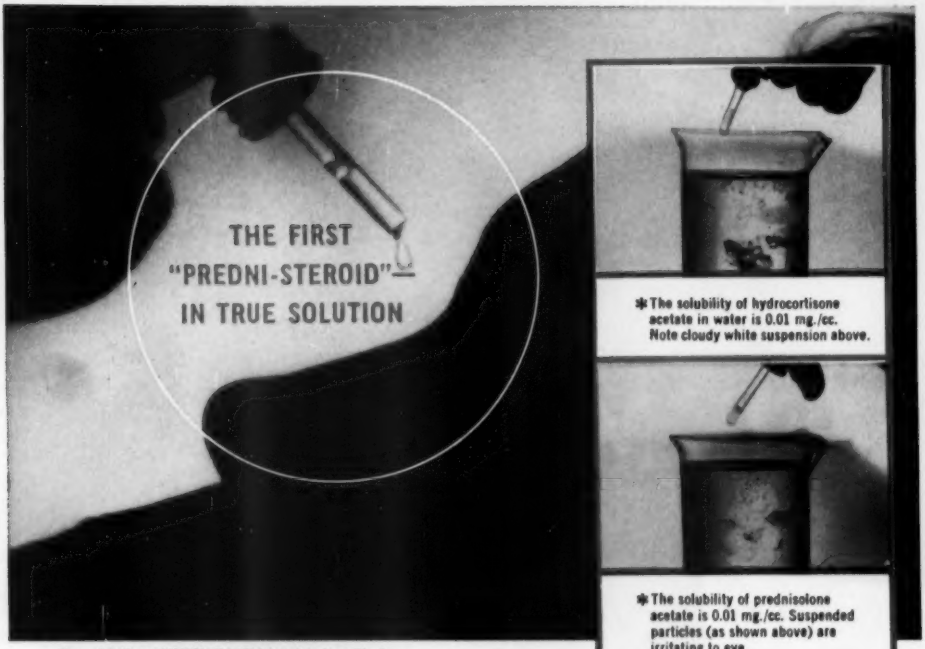

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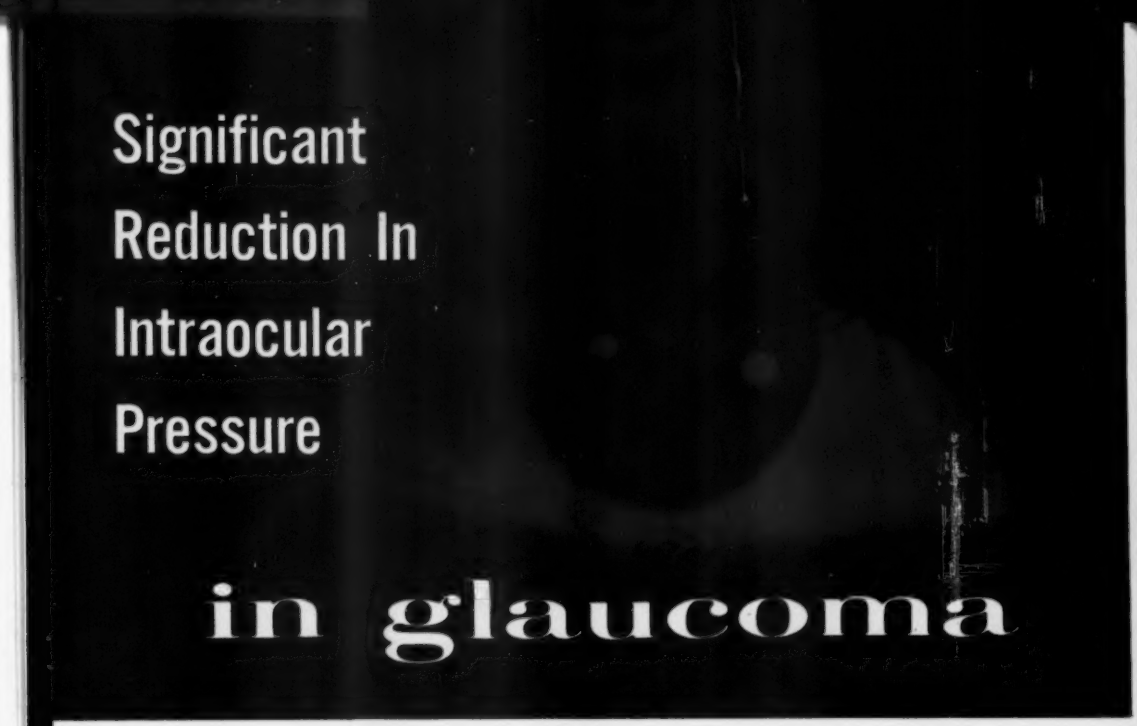

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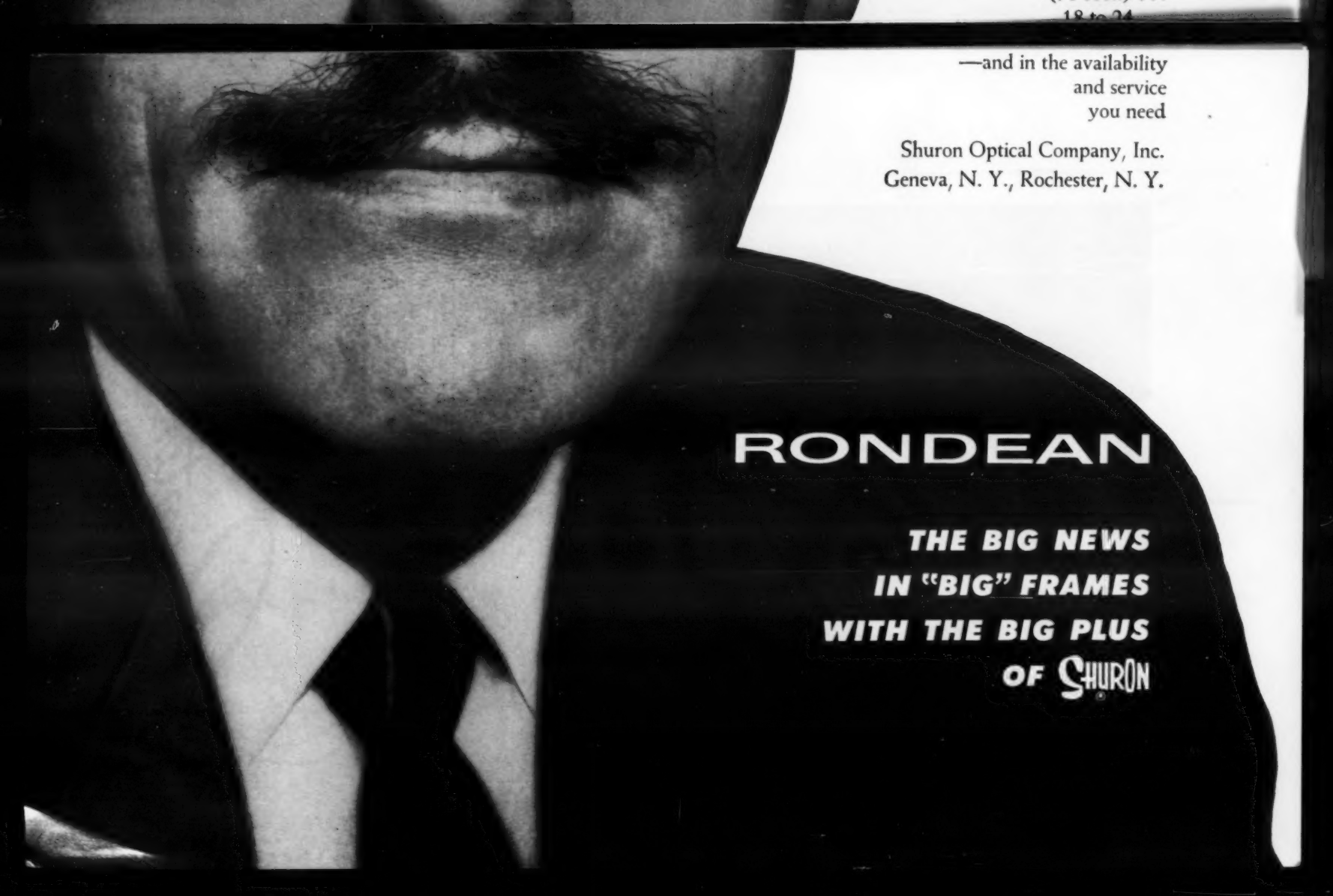
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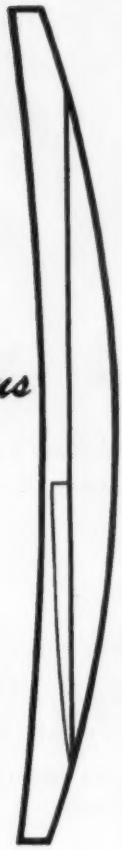

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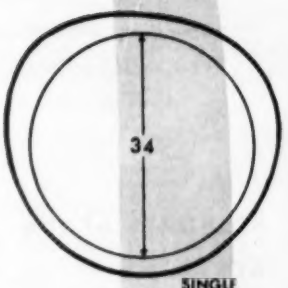

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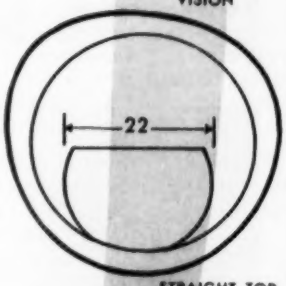

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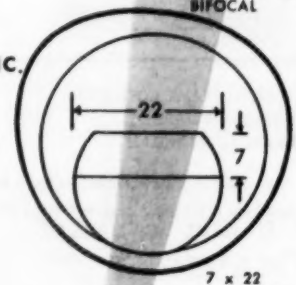

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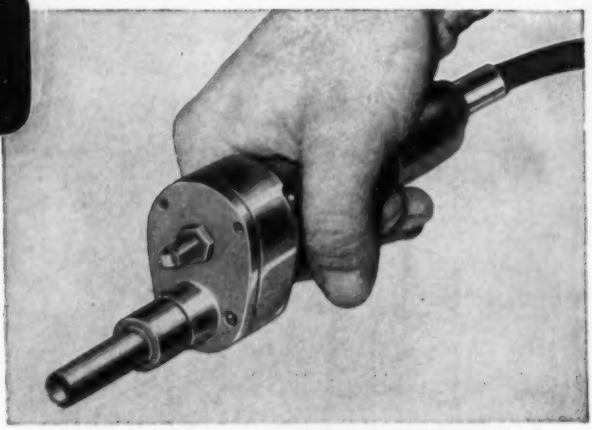

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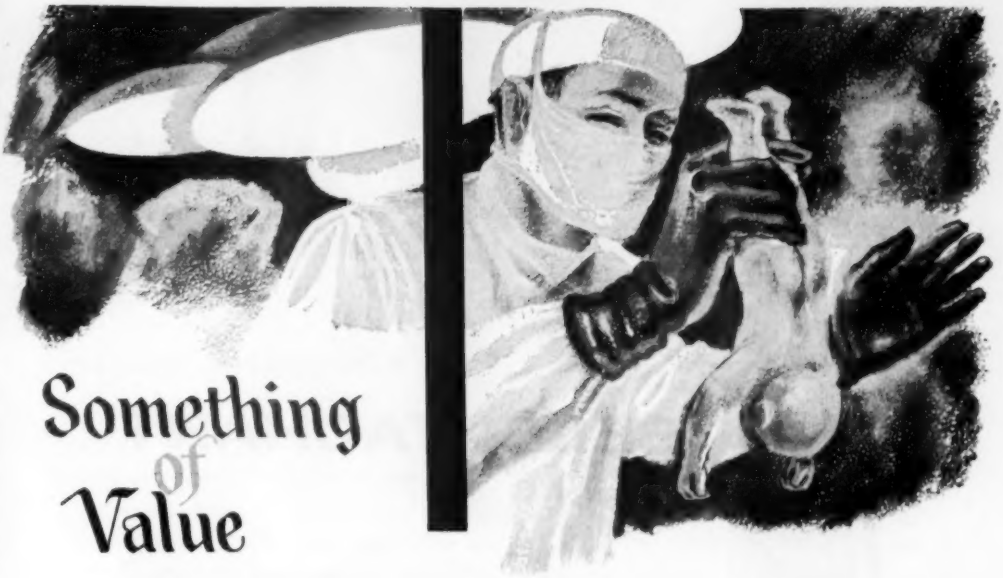

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A.M.A. ARCHIVES OF
OPHTHALMOLOGY

Circinate Retinopathy

Part I

WILLIAM R. HOUSTON, M.D., and GEORGE N. WISE, M.D., New York

In 1893 Ernst Fuchs [1] first reported as an entity a group of 12 cases, 8 of which he considered typical. He coined the term retinitis circinata to describe them, for the retinal picture strongly brought to mind the skin lesion herpes circinatus (tinea circinata).

These cases occurred predominantly in elderly women and involved one or both eyes in a chronic disease process. All showed a gray or yellow-gray macular discoloration encircled by a zone of small discrete or larger coalescing white spots, with an intervening relatively normal retinal area. The central discolored area was small at first but later became disc-sized or somewhat larger. It had no sharp boundary and at times appeared slightly raised. There was minimal or no pigment proliferation seen in these cases. The incomplete ring of white faintly glistening spots was always deep to retinal vessels. Ageing spots became dirty white. The central changes persisted and gave rise to a scotoma with permanent visual reduction. The circinate girdle was sometimes a transient phenomenon. Hemorrhages, when present, were usually small and point-like. Occasionally larger hemorrhages did occur.

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Historically, considerable controversy arose over priority in first describing this condition. Hutchinson's report [2] in 1876, though slightly suggestive, probably did not describe Fuchs' retinitis circinata.[1-3]

De Wecker and Masselon's three cases,[5] which they called *dégénérescence graisseuse*, probably did represent the same condition Fuchs was to describe two years later. Indeed, Fuchs agreed that their illustrated case was one of his type.[1]

The year after Fuchs' publication, De Wecker [6] claimed to have seen 15 such cases, the first in 1873. He called the condition *dégénérescence blanche* (associated with *dégénérescence graisseuse*). Several years later De Wecker [7] noted the similarity in infants between retinitis circinata and some gliomas. One such eye enucleated for glioma, which he considered had retinitis circinata, unfortunately had no microscopic report.

Finally, Goldzieher in 1887 [8] and again in 1889 [9] and 1897 [10] reported cases of "Hutchinson's changes" at the macula with a wreath of exudates about them. Fuchs [1] doubted that these were cases of his retinitis circinata. Nettleship [4] agreed with Fuchs and believed that both Hutchinson and Goldzieher were describing colloid nodules of the elastic lamina (Tay's choroiditis).

Seven cases of retinitis circinata have been examined microscopically. Ammann [11] performed the first such examination in

1897, upon an eye with gray macular discoloration surrounded by shining white spots. In cross section the macular retinal area was four times its normal thickness. The external plexiform layer was especially thickened and contained fat granule cells, partly in long rows and partly in very large vacuoles. The outer nuclear and rod and cone layers were missing. Muller's sustentacular fibers were thickened. At the macula were extravasations of blood, hyaline plates, and fibrinous material. There was medial thickening of the choroidal vessels.

Ammann believed that the white spots seen ophthalmoscopically were fat granule cells in clusters which appeared at old hemorrhage sites. These fat granule cells he considered mononuclear cells, originating from endothelial cells and capable of phagocytosis. Others [12,13] have thought this to be a questionable case of retinitis circinata.

Morax reported the second case [14] in 1926. Microscopically the choroid, pigment epithelium, and rod and cone layers were normal. Spaces were present in the external plexiform and inner nuclear layers. Clear ovoid cells which corresponded to the ophthalmoscopically visible white spots were seen. This case also has been called questionable.[15]

Seefelder's case [16] presented a typical ophthalmoscopic picture of retinitis circinata in one eye and senile macular disciform degeneration in the other. He found the girdle of spots composed of fatty granular cells chiefly in the outer plexiform and the nuclear layers. Cystoid retinal degeneration was present, with the disappearance of the outer plexiform and rod and cone layers, and fatty hyaline deposits were occasionally seen. The pigment epithelium was markedly degenerated, and between it and the choroid was a connective tissue thickening with a choroidal blood supply. These macular changes have subsequently been considered characteristic of disciform degeneration.[17,18]

Ophthalmoscopic examination in Wölfflin's case [19] revealed a senile disciform macular degeneration and a circinate figure of yellow white plaques about it. Many small round hemorrhages were present. Microscopically, the choriocapillaris had largely disappeared. The macular retina was three to five times normal thickness. There was a neovascular fibrosis between the lamina vitrea and the outer nuclear layer, elevating the macular retina. The pigment epithelium revealed degeneration, migration, and proliferation. Corresponding to the circinate figure were cystic spaces containing fibrin and hyalin in the outer nuclear layer. Special fat stains were not used. The other eye was entirely normal ophthalmoscopically, but microscopically it revealed loosened pigment epithelium in several places and a few circumscribed cicatrizations between retina and choroid in peripheral zones.

Schneider [20] examined microscopically the eye of a 25-year-old man with glaucoma following a retinal detachment. Five years previously, this eye had revealed a gray macular area with a white-spot girdle and hemorrhages. Microscopically the central retina was five times normal thickness, contained fat-filled cystic spaces, and showed an occasional degenerated pigment cell. The pigment epithelium and rod and cone layers were destroyed, and the outer nuclear layer was partly destroyed. Sections of lamina vitrea were lacking in the areas of pigment epithelium defects. There was new connective tissue between the retina and choroid in one area. Widening of the central retinal vein and a rich increase in the optic nerve vessels were present. This finding was not further explained but suggests to us central vein obstruction.

Loewenstein and Garrow [21] saw an extramacular semicircle of retinitis circinata below the optic disc in a 63-year-old man blind from simple glaucoma. A piece of the retina with circinate changes, stained with scarlet red, was examined microscopically. There was a nonfatty substance in large spaces corresponding to the outer plexiform layer. Fatty droplets with no visible nuclei were seen throughout the entire retinal thickness. Fat sheathing of the larger vessels passing through the girdle was seen. Vessel walls

were thickened. Capillaries were narrowed and dilated locally, forming aneurysmal ectasias with fatty wall changes.

Both eyes of an 80-year-old woman with almost identical histologic secondary senile macular degeneration were examined microscopically by Klien.[18] Only the right eye showed a circinate figure ophthalmoscopically. The first change in this right eye was a macular pigment disturbance, followed by circinate changes about it. Just before death a 2 D. elevated grayish-white lesion of cystic appearance was seen in the right macula. Many fine blood vessels appeared to grow into this lesion from the adjacent retina. Microscopically a mound of connective tissue elevated the macula and lay between the lamina vitrea and a band of cuticular substance thought to be a product of the pigment epithelium. New vessels—mainly from the retina—came through many breaks in this cuticular band. There was a cyst in the foveal area. Fatty granular cells were present in the middle and outer retinal layers. Fibrous tissue and capillaries grew from the choroid through two breaks in the lamina vitrea. Neovascularization from retinal capillaries was observed clinically and histologically in this case. The eye not showing circinate changes lacked an equal degree of perimacular vessel sclerosis.

These seven microscopically studied cases presented strikingly similar findings of marked retinal thickening, cystoid retinal degeneration, and fatty degeneration with fatty granular cells. The above probably began in the external plexiform layer and were followed by the destruction of the adjacent layers and the rods and cones. The pigment epithelium usually degenerated, migrated, or proliferated. Often there was a new-formed connective tissue mass externally in the retina. Aneurysms and neovascularization were reported in some cases. The association of circinate figures with disciform macular degeneration and secondary senile macular degeneration was noted. The major changes were in the external retinal layers, either at the nutritional junction of the retina and choroidal blood supply or entirely in the choroidally supplied portion.

Over 120 reported cases of retinitis circinata have been reviewed.[1,2,6,8-14,16,18-75] These cases were classified under three headings: probable, questionable, and doubtful. Fewer than half of the cases reviewed appeared to fall definitely within the confines set down by Fuchs. Many cases were incompletely described and followed; few were illustrated.

A few broad generalizations can be made from this review. Omitting the doubtful group, retinitis circinata was twice as frequent in females as in males. The average age incidence was in the 50's and 60's, the average age of the men being a few years younger than that of the women. These averages indicated retinitis circinata to be a disease predominantly of older age, although there were reports of cases in young adults and children.

The spots of the circinate girdle were variously described as white, glistening white, dull white, dirty white, yellow white, and yellow. The macular lesion was described as white, yellow, gray, cloudy, muddy yellow—gray, and hazy gray. Disturbance of pigment was sometimes noted. The optic disc, when mentioned, was usually normal; however, a few were described as being slightly pale or having indistinct borders. In those cases with field examinations, central scotoma was usual. Hemorrhage occurred in over half of the cases in which it was mentioned.

Central vision was markedly reduced and remained so, regardless of the further course of the circinate figure. Even when the circinate figure disappeared, the central vision did not improve.[76]

Comment

The diagnosis of circinate retinitis through the years has grown away from Fuchs' original description. Not only have macular lesions not fitting his specific criteria been labelled circinate retinitis but extramacular ring lesions have also been

given this name. Furthermore, 30 years after Fuchs designated retinitis circinata an entity, senile disciform macular degeneration was clearly set forth, and it now appears that many cases described subsequent to Fuchs as retinitis circinata actually belong to the disciform group. Indeed, it is extremely rare to find a case today which exactly fits his description.

A clinical diagnosis of Fuchs' retinitis circinata depends upon two factors: a definite macular lesion and a typical circinate figure encompassing it. Both factors must be or must have been present before the diagnosis can be made. The circinate figure is typical and obvious clinically. The central macular lesion is considerably less definite and presents the major difficulty. Simple review of the literature leads one to doubt the specificity of Fuchs' retinitis circinata as an entity.

In our clinical experience the central macular lesion was a protean finding in cases we originally considered clinically typical of Fuchs' retinitis circinata. Subsequent examination of such cases showed them actually to be examples of senile disciform macular degeneration with circinate figure or early stages of Coats' disease. In one case a central circinate lesion was secondary to "silent" central retinal vein obstruction, the latter diagnosis only becoming evident four years later. Indeed, several cases of the classic circinate phase of diabetic retinopathy could have easily been considered Fuchs' retinitis circinata on clinical appearance of the central lesion alone.

Although the central macular lesion was controversial, the surrounding circinate figure rarely was. In our clinical experience the circinate figures seen in disciform macular degeneration, multiple miliary aneurysms with retinal degeneration, diabetic retinopathy, occasional lesions of Coats' disease, and following venous obstruction, in rarer instances, have all been clinically identical or so similar as to indicate a common pathogenesis. These rings have been seen both at the macula and extramacularly. Regardless of site, they have presented much the same picture, though varying often in degree.

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Circinate Retinopathy

Part II

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This section will be devoted to both macular and extramacular circinate lesions as seen in venous obstruction, diabetic retinopathy, Coats' disease, Leber's disease (multiple miliary aneurysms with retinal degeneration), and senile macular disciform degeneration. The various findings such lesions have in common will be noted, and a possible pathologic sequence in their formation will be suggested.

Venous Obstruction

Jensen [1] described circinate lesions seen after branch venous obstruction as a perimacular zone of white exudate separated from a central yellowish-gray discolored area. He thought these were rarely occurring secondary phenomena most frequently preceded by hemorrhage. Seventeen of his sixty-one cases of branch venous obstruction showed circinate infiltrates. Some appeared as early as two months after the obstruction. Later, as they became more fully developed and typical, the exudates coalesced and lobed figures were formed. These circinate figures were sharply outlined, varied in size, appeared singly or in groups, and were located predominantly about the posterior pole of the eye. They were seen both outside and inside the territory of the obstructed vein. Macular pigment changes at the center of the lesion prevented Jensen from telling whether the changes in this region were or were not characteristic of Fuchs' retinitis circinata. The exudate rings tended to disappear in time; one disappeared six months and another three years after first being observed.

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Others [2,3] also mentioned circinate figures after venous obstruction, without further description.

We examined clinically such circinate lesions occurring after branch or central vein obstruction. Most developed near the macula or disc; several appeared peripherally. They occurred singly or in groups and developed only in previously obstructed areas. The various-sized ring or arc figures of inert yellowish-white exudates surrounded a central aneurysmal cluster. Discrete exudates on either side of the coalescent ring gave it an archipelago appearance. The retinal zone between the ring and the aneurysms was conspicuously free of exudation. This zone was sometimes narrow and at other times rather broad. Some aneurysms appeared older and more hyalinized than others. At times central aneurysms were clearly visible, while at others there was a thin grayish haze over them. Occasionally a slightly elevated gray tissue almost obscured their view. This haze or denser gray tissue was undoubtedly preretinal fibrosis.

Such a circinate lesion was described microscopically by Loewenstein and Garrow.[4] In their case of chronic glaucoma a circinate lesion suddenly developed below the disc just prior to enucleation. This eye was suspected of harboring an intraocular tumor, and repeated fundus examinations had been made before the circinate lesion appeared. No antecedent hemorrhage was noted.

Microscopically the lesion showed aneurysms, obliterated and dilated vascular channels, new blood vessels, and a delicate preretinal gelatinous tissue containing a few thin-walled neovascular channels. The

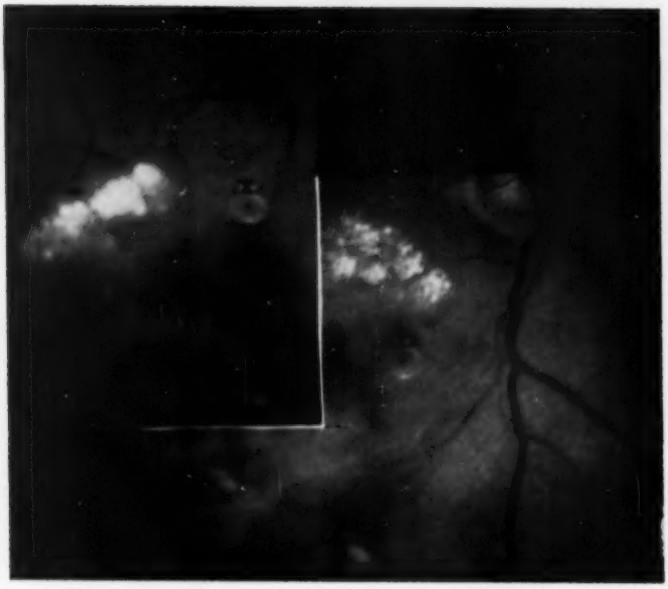

Fig. 1.—Man, aged 54. Classic obstruction of a branch of the inferior temporal vein O. D. Corrected vision 20/50. Picture taken four months later, showing residual hemorrhages and obstructed area and the beginning of circinate exudate at lesion border. Corrected vision 20/30. (See Wise,[40] Figures 3, 4, 5, and 6.)

capillary endothelial cells contained lipid droplets identical with those reported by Ballantyne and Loewenstein [5] as the earliest microscopic change in diabetic retinopathy. The outer plexiform layer was abnormally broadened, with cystic spaces containing a nonfatty exudate. Collections of fatty granular cells, some in all retinal layers, made up the girdle about the lesion.

Ballantyne's [6] microscopic study of the disc and optic nerve in this same eye revealed central retinal vein obstruction due to endothelial proliferation and collateral vascular channels about the block.

Diabetic Retinopathy

Fuchs [7] noted the similarity between retinitis circinata and what is now called the circinate phase of diabetic retinopathy. However, he thought that the diabetic exudates were never so large nor the architecture of the ring so complete as in his retinitis circinata.

Many authors [8-13] reported diabetic exudates often forming a rough circle around the macula, and a few [14,15] described complete rings.

Edgerton [16] believed that the circinate phase of diabetic retinopathy indicated concurrent Fuchs' retinitis circinata.

Although little has been written on the circinate phase of diabetic retinopathy as such, its marked similarity to Fuchs' retinitis circinata was appreciated from the beginning.

The circinate phase of diabetic retinopathy occurred in 9% of Hanum's [14] large diabetic retinopathy series and in 10 of Ballantyne's 51 cases.[13] The vast majority of Hanum's 9% had rings about both maculae.

The exudates we saw in circinate figures following venous obstruction were often clinically identical with those of diabetic retinopathy. Similar vascular cuffing by the exudates was observed in both. After venous obstruction, and in several cases of diabetic retinopathy, identical extramacular rings with central aneurysms were noted. These findings suggested a study of diabetic retinopathy to determine the relationship between microaneurysms and exudates.

In diabetic retinopathy, Ballantyne [13] found exudates always following aneurysms, never the reverse. Our retinal slit-lamp study of fundi showing moderately severe

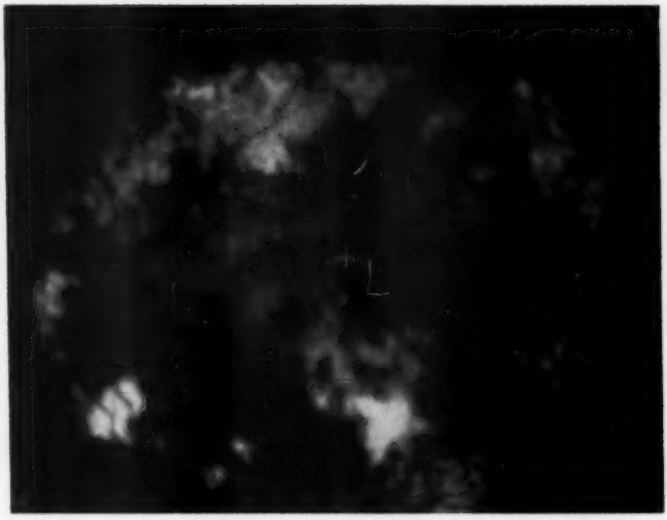

Fig. 2.—Man aged 64. Diabetic retinopathy with central circinate lesions O. S. Corrected vision 20/60 (See Wise,[20] Figures 7A, 7B, and 8.)

diabetic retinopathy revealed an even closer relationship. The exudates were not scattered indiscriminately over the fundus but bore a definite relationship to the microaneurysms. Actually, the exudates formed innumerable ring and arc figures centered on microaneurysms. Not all clusters of aneurysms had arcs or rings about them, and some arcs failed to show central aneurysms. The small number of clinically visible aneurysms as compared with the number actually present microscopically could explain this. There were far too many arcs and rings of exudates containing central aneurysms for this observation to be incidental.

Many more arcs than complete rings were seen. The compactness of such lesions probably accounted for this configuration. The arc or ring patterns, pressed together as they were, sometimes resembled a curlicue iron grillwork.

In diabetic retinopathy Ballantyne [13] described microscopically wide, dilated neovascular channels of capillary structure growing through the internal limiting membrane into the vitreous. They had a delicate fibroblastic supporting mantle and appeared to pierce the internal limiting membrane freely. The fibrous matrix was extremely delicate at first but became heavier and more definite later. These new vessels developed from obstructed capillaries and small venous radicles. Antecedent hemorrhage was not a causative factor in their development. Ballantyne labelled this phenomenon rete mirabile retinitis proliferans.

While most of the exudate rings we observed contained central aneurysmal clusters, others had at their center both aneurysms and patches of rete retinitis proliferans. Indeed, one such ring contained an arborizing rete proliferans connected with a spray of intravitreous neovascularization. The latter originated from a large nearby obstructed retinal vein.

Ballantyne and Loewenstein [5] and Ballantyne [13] studied the microscopic changes in diabetic retinopathy. The exudates occupying large cystic spaces in the outer plexiform layer were composed of an albuminous or hyalin matrix surrounded by a lipid zone. Those exudates more superficial and often seen cuffing retinal vessels were composed of fatty granular cells. These same cells appeared to a less extent scattered in all retinal layers. Capillaries, particularly deep ones, were dilated, ectatic, or obliterated with hyalin change of their walls. Capillary endothelial cells were swollen and laden with

lipid droplets. Aneurysms were profuse. As in the circinate figures following venous obstruction, exudates had a coalescent tendency. In general, the major degenerative changes occurred in the deeper retinal layers.

Thus, both clinically and microscopically these very common diabetic ring lesions were practically identical with those much rarer circinate lesions occurring after venous obstruction.

Coats' Disease and Leber's Disease

Coats [18-20] described a protracted disease of the young characterized by extensive deep retinal and subretinal exudation and hemorrhage. Those cases with marked vascular changes progressed, while those without such changes tended to self-limitation.

Microscopically, there was subretinal neovascular connective tissue, loose early and heavier with fewer vessels later. Marked edema, cystic degeneration, and often total destruction characterized the outer retinal layers. Massive subretinal exudation described as rich and mixed with fibrin and blood was typical. Vascular changes, predominantly of the veins and capillaries, consisted of obstructions, ectasias, dilatations, diseased vascular walls, perivasculitis, neovascularization, and a variable number of aneurysms. Arterial involvement was often minimal and sometimes even absent. Retinitis proliferans into the vitreous was occasionally seen, but most neovascular proliferation was subretinal.

Coats' thought that the disease started with hemorrhage from the deep capillary bed. Later, this broke through into the subretinal space. Fibroblastic vascular organization of this blood and its sequellae completed the sequence.

Occasionally ring figures about these lesions were noted, but they were not further described.

Leber [21-23] also described a condition of the young characterized by multiple retinal miliary aneurysms leading to retinal degeneration. He believed this to be an entity representing one of Coats' types. The multiple aneurysms occurred in small or widespread groups predominantly at the posterior pole of the eye. At times they were centered at the macula. A girdle or broken arc of white exudation often encircled the aneurysmal cluster at a varying distance from it. The exudative ring was usually deep to retinal vessels but when extensive could involve them. Most aneurysms appeared within the circinate figure, but they were also seen outside.

Leber noted a similarity of his disease and Fuchs' circinate retinitis, but he thought that they differed. His occurred in young men and showed macular pigment, while Fuchs' cases had little or no pigment disturbance and appeared predominantly in older women.

Most of Leber's cases showed microscopic findings the same as those reported by Coats.

In general, Leber probably saw earlier cases than Coats; his cases showed more aneurysm formation, were more likely to show circinate figures, were less severe, had less exudation, and microscopically showed more new vessel formation in the inner retinal layers.

Leber insisted that his was primarily a toxic or embolic arterial disease in which hemorrhage was of secondary importance. Coats believed that his cases were due to the organization of hemorrhage from diseased capillaries and veins.

The persisting controversy between Coats and Leber adherents has no place in this report. For the sake of clarity both conditions will be considered variants of the same pathologic sequence, and called in this article Coats' disease. It is not, however, implied that they necessarily have the same etiology.*

Circinate lesions in Coats' disease have been reported by others.[24-27] Usually these consisted of large and heavy exudative rings surrounding areas of less exudation containing aneurysms. Reese [28] reported a case of Leber's disease—called by him retinal telangiectasis—which was later diagnosed as Eales' disease. The importance in cir-

* For a complete discussion of this see Wise.[29]

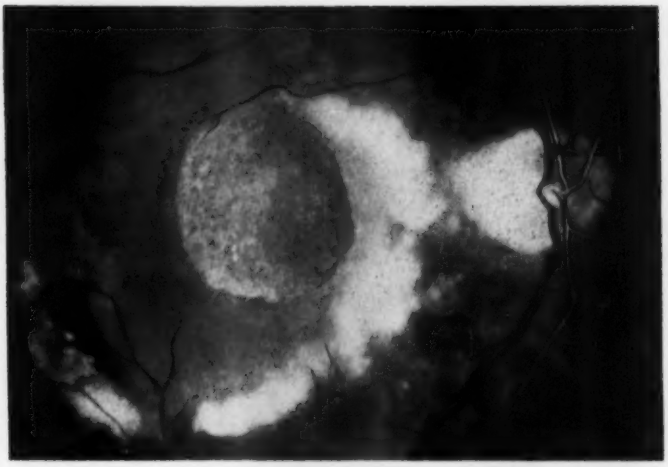

Fig. 3A.—Man aged 77. Vision O. S. failed about 20 years ago. Vision O. D. failed five to six years ago. O. D. showing classic senile disciform macular degeneration with circinate exudates. Retouched photograph.

Fig. 3B.—Same patient as in Figure 3A. O. S., showing extensive Coats' disease. Retouched to show vascular cuffing and cholesterin crystals.

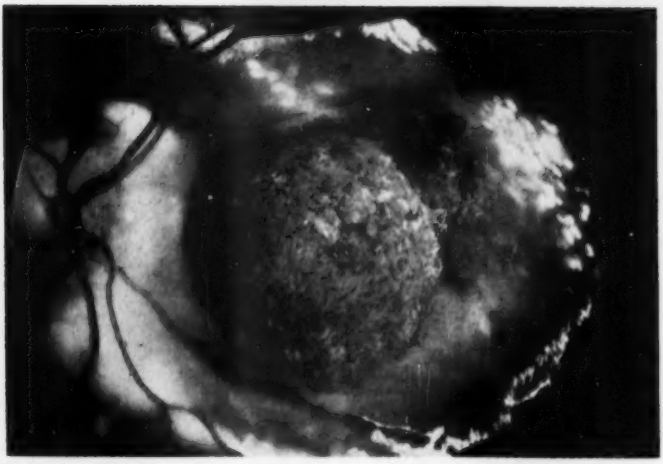

Fig. 4.—Woman, aged 69. Slowly progressive visual loss O. D. for past three to four years. Patient had peripheral massive areas of yellow-white exudate and three circinate lesions at the posterior pole, one being directly at the macula. Retouched photograph to show the circinate lesion just nasal to the disc. There were several aneurysms just inside the exudative ring at 7 o'clock, not shown in the photograph.

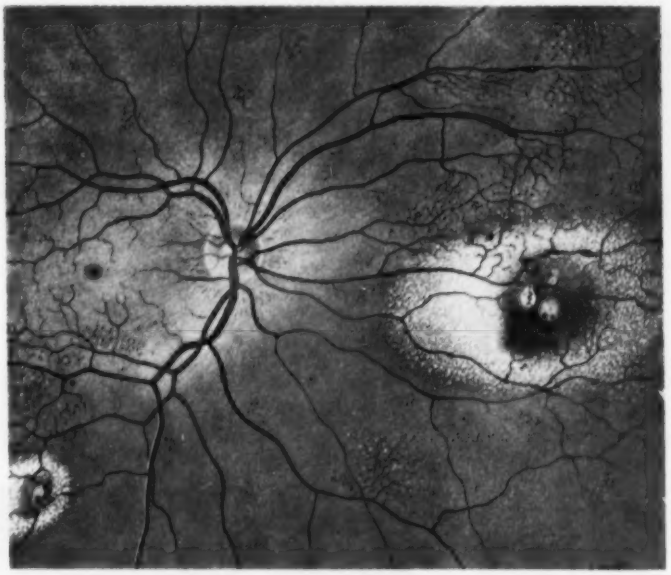

Fig. 5.—Youth, aged 17. Classic Leber's disease with two circinate lesions O. D. Note central tufts of fibrotic proliferation into the viterous in both rings, also periarterial neovascular free zone just below the macula. Of three apparent arteries containing aneurysms, two were definitely abnormal arteriovenous communications.

cinate lesions of capillary or venous obstruction and the intimate association of the latter with Eales' disease [29] could be significant. Others [27,30-32] have reported cases of circinate retinitis which progressed to Coats' disease. The association of the two diseases has thus been long noted.

The exact pathology of the Coats' circinate lesion has not been specifically studied. However, most authors reported these rings about areas of severest retinal involvement. Therefore, microscopic study of these most intensely involved zones should give a close approximation of the central lesion pathology. Similarly, no specific study has been made of the exudative ring. Since it is composed clinically of the widespread exudative material, microscopic study of the latter should indicate its composition.

On this hypothesis, then, the central lesion included obstructed capillaries and small vascular radicles, dilated vascular channels, new blood vessels, aneurysms, preretinal fibrosis, and, infrequently, delicate new vessels on the inner retinal surface. The deeper layers were edematous and cystic.[21,26,28,33-38] Similarly, the exudative ring was composed of serofibrinous exudate and fatty granular cells.[34-37]

In this way the close microscopic similarity of these Coats circinate lesions to those previously discussed is made apparent.

We observed one classic case of Leber's disease in the right eye of a 17-year-old youth. Both arterial and venous aneurysms were present, but the latter tremendously predominated. Two circinate lesions were present, one below the macula and a larger one several disc diameters along the inferior nasal vessels. Both contained central microaneurysms and small retinal hemorrhages. At the center of each was a tuft of preretinal fibrosis containing a few fine new vessels. The two circinate figures were composed of dirty yellowish-white exudates. These were predominantly deep to retinal vessels but in some places rose to their level and cuffed them. Discrete border exudates gave the confluent ring an archipelago appearance.

We also observed circinate lesions in Coats' disease. These were usually large and rather variable. One had such heavy central exudation that detail of this area was obscure. Its heavy border ring of exudate had a dirty dark discoloration, probably from admixture with blood. Small discrete white exudates peppered the outer ring border.

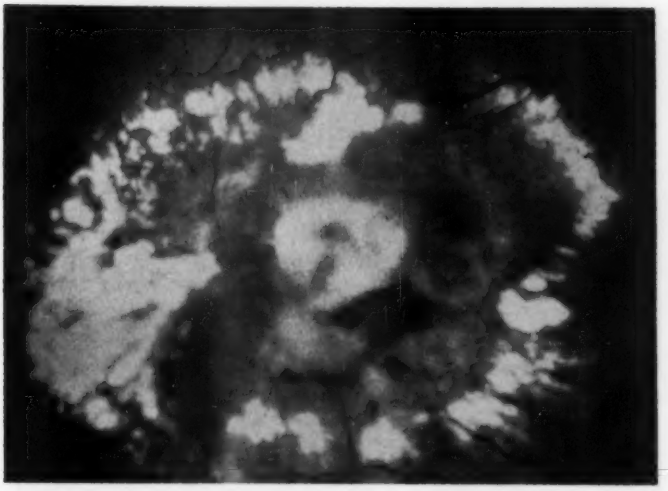

Fig. 6.—Woman, aged 76. Lost central vision O. D. five to six years previously. Fundus O. S. showed granular macula. O. D., showing raised mound at macula with pigment proliferation and circinate exudates. Note cuffing of vessels by exudate. While this is undoubtedly a senile disciform macular degeneration with circinate ring, it came nearest to fitting Fuchs' original description of circinate retinitis.

Another formed a scalloped three-quarter ring at the border of a heavy exudative sheet. The center of this area had a dirty faintly red fundus reflex, too hazy for detail. Still others, having less central exudation, showed clusters of aneurysms and intermingled hemorrhages surrounded by rings of heavy yellow-white or dirty exudation. Clinically, these ring lesions were very similar to those just described in our classic case of Leber's disease. Generally, our Coats' circinate lesions had a much larger and more heavily exudative ring figure, while the central areas were often obscured by moderate to heavy exudation and hemorrhage. The mixture of blood in such regions gave a variety of colors.

Taking into consideration the heavy exudative and hemorrhagic nature of Coats' disease, its circinate figures still show many clinical features observed in the ring lesions previously discussed.

Senile Disciform Macular Degeneration

Junius and Kuhnt,[39] in 1926, first established the condition now usually known as senile disciform macular degeneration. Verhoeff and Grossman,[40] in an excellent review

Fig. 7.—Man, aged 73. Senile disciform macular degeneration O. S. with circinate exudates. Note vein dipping into central mound. Retouched photograph.

Fig. 8A.—Woman, aged 75. Senile disciform macular degeneration with circinate ring O. D. Corrected vision 3/200. Two aneurysms and cholesterin crystals were seen in the exudative ring.

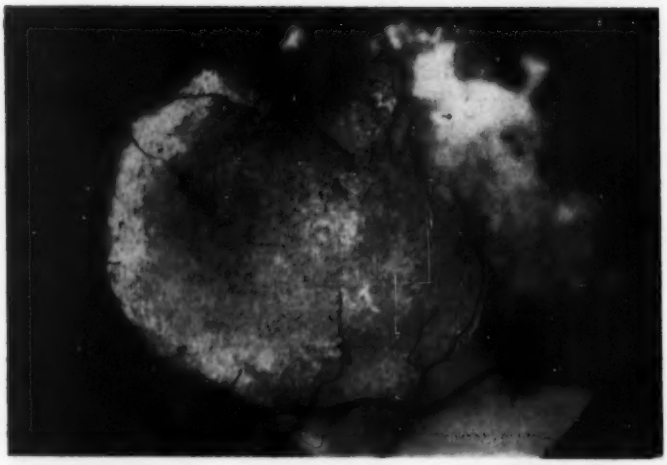

Fig. 8B.—Same patient as in Figure 8A. Senile disciform macular degeneration O. S. with circinate exudates. Corrected vision 3/200. Note large vein dipping into central elevated mound. Retouched photograph.

of this disease, gave credit to Pagenstecher in 1875 for the first recorded case.

It has been described by many [39-47] as a disease of the elderly, either unilateral or, often, bilateral, with insidious or more sudden onset. Following macular changes much like ordinary senile macular degeneration, some cases started with subretinal macular hemorrhage causing an oval raised dark central mass. Others were initiated by massive deep retinal or subretinal white or yellowish-white macular exudation. Hemorrhagic cases shortly entered an exudative phase, as a rule, and became white or yellowish-white. The lesion borders were commonly sharp. Sometimes, vaguer borders had extension fading toward the peripheral retina like the tail of a kite. The mass was always deep to retinal vessels. It was variably raised to 6 D. and often had a dimple at its summit. Sometimes enlarged retinal vessels dipped into the mass near its highest elevation. Arterio-

Fig. 9.—Woman, aged 66. History of poor vision O. S. for one year. Corrected vision 4/200. The central macular area shows scarring, exudates, and hemorrhages but is not measurably raised. Classic circinate exudates about the macular lesion. Note similarity of this to Haab type of senile macular degeneration. Retouched photograph.

venous communications were noted in a few cases. In other lesions such vascular abnormalities were absent. The mass varied in size from smaller than the disc to several times its area, but it only rarely extended beyond the vascular arches above and below the macula. Over a period the mound tended to "settle" and scar, showed pigment proliferation, and became whiter in areas. Some lesions were surrounded at one time or another by a white or yellowish-white circinate figure—usually incomplete. Descriptions of this ring indicated that it was clinically identical with that of Fuchs' retinitis circinata. Intermediate forms with partial rings and, commonly, cases without rings were recorded. The retinal vessels, disc, and periphery showed no significant change. Central vision was permanently lost.

From the beginning, the interrelationship of Fuch's circinate retinitis, disciform macular degeneration, and Coats' disease has been widely argued. As noted in Part I, it was often difficult in reviewing reported cases of Fuchs' circinate retinitis not to believe many of these to be actual cases of disciform

Fig. 10.—Woman, aged 76. This patient began with a bilateral senile macular degeneration—Haab type. Over a period of several years the central area of the right eye became more exudative and a circinate lesion developed around the macula. The exudative disease progressed around the disc and finally throughout the entire fundus so that when last seen, there was the typical appearance of widespread Coats' disease in this eye. Retouched photograph to show cholesterin crystals in the circinate ring about the macula.

macular degeneration with circinate figure.[48-54] Fuchs' description[7] preceded those of Junius and Kuhnt[39] and Coppez and Danis[44] by more than 30 years. This undoubtedly accounts for some of the confusion.

A case showing circinate retinitis in one eye and disciform macular degeneration in the other was reported.[55] Classic circinate figures about disciform macular lesions were frequently noted.[26,39,41,42,44,45,47] The similarity of circinate retinitis and disciform macular degeneration was also expressed.[42,44,56-58] Some believed that these two represented different phases of the same lesion.[39,44,58] Tails from degenerative disciform lesions extending into the periphery were reported,[44,45,59] and Davenport[45] noted their similarity to the exudative tongues seen in Coats' disease. Elschnig[56] believed that circinate retinitis and Coats' disease were definitely connected, and Fisher[41] reported a case with Coats' disease in one eye and both circinate retinitis and Coats' disease in the other. Reese[60] noted the similarity of his massive retinal fibrosis, disciform macular degeneration, circinate retinitis, and Coats' disease. His first case of massive retinal fibrosis showed a circinate figure. He also reported two cases of Leber's disease—called by him retinal telangiectasis—which progressed to Coats' disease.

The difficulty of clinical differential diagnosis between some cases of circinate retinitis and senile disciform macular degeneration is familiar to all. Their often identical circinate figures add to this problem.

The microscopic reports of disciform macular degeneration, while not being as varied as the etiologies suggested, have not all been exactly alike. Analysis of these reports[40,56,57,59,61-63] for pathology previously shown in other circinate lesions, showed that all presented neovascularization and fibrosis in the central zone. Two reported cystic degeneration in the outer plexiform layer. Two described fatty granular cells, and one noted sclerotic alterations of the capillaries and precapillaries in the perimacular deep retinal layers. While no aneurysms were mentioned, only Klien's report[57] was published since the recent intense interest in retinal microaneurysms. The latter are difficult to demonstrate in ordinary tissue sections and usually require special techniques for identification.

Klien's paper[57] deserves special mention. She followed her patient clinically and later obtained both eyes for microscopic study. At first both maculae showed a slowly progressive senile degeneration with decreasing vision over a two-year period. Within the next four years the right eye developed a central disciform degeneration with circinate figure and severe loss of vision. The left eye had a much more slowly progressive flat senile macular degeneration without a circinate figure. Microscopically, the latter revealed hyalinized small retinal arterioles with reduced apertures and thick-walled deep and superficial retinal capillaries, especially at the macula. The central pigment epithelium and some central rods and cones were missing. Only a few nuclei appeared between normal retinal limiting membranes at the fovea. An occasional fibroblast was seen on Bruch's membrane behind the macula. On the other hand, the eye with disciform degeneration and circinate figure showed much more advanced sclerosis of the retinal macular capillaries and precapillaries. This macula was elevated by a mass of connective tissue, new vessels, and thickened cuticular substance with cystic retinal degeneration above. Clumps of fatty granular cells in the middle and outer retinal layers made up the circinate figure.

Indeed, Klien considers all circinate figures to be composed predominantly of fatty granular cells. Certainly our review strongly substantiates this concept.

Klien's[57] description of the circinate figure about a disciform-type lesion was identical both clinically and microscopically with that of lesions described in other conditions in this report.

We found only two microscopic reports [57,63] of disciform degeneration with clinically observed circinate figures. One of these [57] had central findings similar to those circinate lesions herein reported in other conditions, except for the absence of aneurysms. Our 16 cases of disciform macular degeneration with circinate figure showed an occasional aneurysm outside the ring once, on its once, on the surface of the central mound once, and on two occasions questionable aneurysms adjacent to the central lesions. Aneurysms are so regularly found associated with retinal neovascularization [29] that special study should reveal them microscopically in this disease.

Thus, although present evidence is not so complete in disciform macular degeneration as is available for circinate lesions with other conditions, it seems apparent that we are dealing with the same lesion in all. Further microscopic study should fill in these gaps.

Comment

Do such similar circinate lesions in these diverse conditions traverse some common pathway in their formation?

Michaelson [64] proposed that embryologic retinal blood vessels develop in response to some unknown factor present in areas of relative retinal anoxia. He showed that all capillaries originated from veins and demonstrated more highly oxygenated arterial inhibition of capillary proliferation. At term the retina becomes maturely vascularized. All retinal areas are thereby adequately supplied with oxygen; the vasostimulating factor disappears, and a state of equilibrium obtains. Michaelson believed that the ability of capillaries and veins to form new vessels did not disappear at birth but simply rested in this state of equilibrium.

It was further proposed [29] that critical degrees of venous or capillary obstruction in the mature retina reactivated Michaelson's embryologic mechanism. Areas beyond the obstruction stagnated and became relatively anoxic. In the embryo the vasostimulating factor in such anoxic areas was regular and preordained. Therefore, orderly vascular development proceeded. On the other hand, venous or capillary obstruction in the mature retina, depending upon its degree, position, rapidity of development, extensions, etc., caused a variable and patchy hypoxia and there followed a variable and patchy distribution of the vasostimulating factor. Under such circumstances disordered neovascularization proceeded primarily from regional veins and capillaries.

It was finally proposed [29,65] that retinal microaneurysms actually represented aborted new blood vessel buds arising in response to this same neovascular stimulus.

Retinal lesions with circinate figures, regardless of the disease in which they occur, have been shown to be clinically similar in many respects and clinically identical in some. Their exudative ring figures have been shown microscopically to consist primarily of fatty granular cells.

The microscopic findings in these central circinate areas strongly suggest regional venous or capillary obstruction or partial capillary obliteration of the deeper retinal network. Arterial obliteration in the retinal end-artery system should lead to infarction, with an entirely different clinical and microscopic picture.

Following such capillary and venous obstruction and its attendant circulatory stagnation, a zone of retinal hypoxia developes. At this point Michaelson's state of equilibrium is disturbed and local vasostimulating factor reappears. Aneurysm formation and neovascularization with its accompanying fibrosis, all predominantly from regional veins and capillaries, mark the local retinal response to this oxygen imbalance. Cystic degeneration in the outer plexiform layer—a regular retinal finding in pure venous thrombosis [66]—is also explained by this mechanism. In the central hypoxic area fatty retinal degeneration occurs. Scavenger cells ingest the fat and move individually toward adjacent normally oxygenated retina. Here they accumulate, forming a ring figure,

until they can be absorbed through unobstructed channels into the general circulation.

The serofibrinous exudation and subretinal hemorrhages of Coats' disease and senile disciform macular degeneration have been omitted from this discussion. The formation of circinate lesions in response to local areas of retinal hypoxia is in no way dependent upon either. The important part they play in the direction of new vessel and fibrotic growth (whether subretinal or preretinal) has been considered in a separate paper.[65]

That venous and capillary obstruction are essential for this pathologic sequence is strongly suggested. Obstruction in pure venous thrombosis is obvious. The venous and capillary obstruction of diabetes and Coats' disease have repeatedly been demonstrated. Klien's careful work has shown deep capillary obstruction over a disciform-type lesion with circinate figure at the macula. Furthermore, circinate lesions without other retinal disease involving venous or capillary blockage have seldom been reported. Even these, if followed sufficiently long, show later evidence of an underlying and previously unrecognized "silent" venous obstruction.[66]

The degree of neovascular formation and fibrosis probably depends upon the severity and suddenness of the capillary or venous blockage and its subsequent local hypoxia. Slowly developing obstructions with lesser degrees of hypoxia and vasostimulating factor should tend to produce delicate fibrosis and aneurysms. More rapidly developing severe and widespread obstruction should similarly tend to produce heavier fibrosis and actual new vessels. In retinal neovascularization fibrosis becomes heavier and contains fewer blood vessels with the passage of time.[29] A special macular propensity to develop fibrosis after venous obstruction also obtains.[66] All of these factors undoubtedly play their part in the variability of circinate lesions.

Since both diabetic retinopathy and Coats' disease are thought to be initiated by widespread patchy capillary disease, the retinal distribution of circinate lesions in these two is understandable.

The predilection of Fuchs' circinate retinitis or senile macular disciform degeneration with circinate figure, whichever one chooses to call it, is less clear. Klien [57] has indicated a selective obliteration of the deep retinal capillaries and precapillaries in this region which could explain it. In the absence of such findings, the proclivity of the macular area to be first involved in slowly developing "silent" central vein obstruction [66] may be of etiologic significance. Certainly, serial cross sections through the region of the lamina criborosa should be obligatory in such cases. Central venous obstructions are much commoner than is generally realized, especially in the older age group, and they will be missed if longitudinal sections only are made.

The scattered appearance of circinate lesions after branch or central vein obstruction is also not clearly understood. Whether this is in any way connected with the variable state of patency of the normal capillary bed at the time of obstruction is purely problematical.

Conclusion

We agree with Loewenstein and Garrow, Bedell,[67] and Klien that retinitis circinata is not an entity as described by Fuchs.

Circinate retinal lesions are manifestations of a local retinal response to hypoxia secondary to capillary or venous obstruction in the involved area.

The pathologic sequence of events under such conditions is suggested.

Dr. Albert Graemiger and Dr. Jaras Shegedyn aided in making the translations; Mrs. Alan Grover made the retouched photographs; Mr. Walter S. Lentschner did the photography, and Mrs. Joyce Rolls gave technical, library, and clerical help. Permission to examine and report the case shown in Figure 5 was given by Dr. E. M. Miller.

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The Scleral Buckling Procedures

1. Surgical Techniques and Management

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Introduction

Gonin is the discoverer of the fundamental principle which governs all rational types of surgery for the reattachment of the retina, namely, that it is necessary and sufficient to permanently seal off all the retinal breaks. As a result of this finding, attempts have generally been made to close the retinal breaks by irritating the choroid lying directly over them. However, Gonin himself and several other authors found that, when breaks were either multiple or large, it was easier to obtain cures by creating a scar which acted as a barrage between the anteriorly located breaks and the more posteriorly situated retina. Such a barrage forms a dyke which limits the detachment to the area surrounding the untreated retinal breaks and protects the portion of the retina which has potential usefulness.

When a correctly performed retinopexy (or simple diathermy operation) results in failure, in spite of what seems to be adequate treatment of all retinal breaks, we feel that the most frequent cause for absence of lasting reattachment is traction exerted on the retina by structures in the vitreous cavity. Such traction either reopens previously existing retinal breaks or creates new breaks, generally located in the vicinity of the treated area. Existence of traction is evidenced by the presence of fixed retinal folds, retinal breaks with rolled edges, and vitreoretinal strands or membranes detected by slit-lamp examination of the posterior vitreous cavity; these alterations have been partly described by several authors and lately by Schepens.[5,7] It was, therefore, natural to think that if the treated choroid were pushed towards the detached retina at the time of surgery, thereby minimizing the effects of traction, a greater percentage of success could be obtained. This idea incited Strampelli to inject blood plasma under the choroid,[10] which he later replaced by a gelatin sponge [11]; Jess [4] used a gauze pad temporarily sutured over the treated area of the sclera, and Custodis [1-3] sutured a piece of plastic material to the treated zone of the sclera without resection. The same thought also led to the development of the scleral buckling procedures.

As a scleral buckling is essentially a modified retinopexy in which the area treated with diathermy is pushed toward the vitreous cavity, the buckle must be placed either over the retinal breaks or, in the case of a barrage, posterior to the retinal breaks. Consequently, detection and accurate localization of all the retinal breaks is an essential step in this type of procedure. In general, the buckled area of the sclera is the only zone to be treated with diathermy; a lamellar scleral resection is often performed in conjunction with the scleral buckling, because it permits the use of very light diathermy upon the thinned sclera and it helps make the choroidal irritation more uniform and the buckle more permanent. Embedding of a foreign body in the sclera creates a higher and more durable buckle.

As the above outline indicates, a scleral buckling differs from a classical scleral resection in several respects. First, the loca-

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tion of the resection is different: In a scleral buckling its location is dictated by the position of the retinal break, whereas a classical scleral resection is generally located in an area which is conveniently reached, slightly posterior to the recti muscles. Second, in a scleral buckling, resection and diathermy are in the same area, which is directly related to the position of the retinal breaks. In a classical resection the diathermy is applied over the retinal breaks but the resection is generally more anterior and is, therefore, less effective than a scleral buckling in pushing the treated area of the choroid toward the detached retina. Finally, in a classical resection no foreign body is used to make the ridge higher and more permanent.

After more than eight years of experimentation and clinical observation, four basic methods of scleral buckling have been developed, each one having its indications, advantages, and disadvantages. More than 1500 operations have so far been performed with these procedures; in our hands they are a great improvement over retinopexy, simple lamellar scleral resection combined with diathermy, and all other techniques we have previously tried. It would be a dangerous error, however, to believe that in the present stage of their development the scleral buckling procedures cause no complications or cannot be further improved. Like other surgical techniques, they will either be perfected or be superseded by more efficient procedures. In spite of the fact that we have had a moderate amount of experience with the buckling techniques, it is with considerable hesitancy that we describe them, because in the course of years these procedures have been repeatedly modified and, it is hoped, steadily improved; our description should, therefore, not be considered as final, but only as the 1957 aspect of techniques which are being actively perfected.

This article covers preoperative care, surgical techniques, and postoperative management; for clarity's sake, the patient's management and surgical techniques have been streamlined to fit standard cases. Difficulties arising in special cases, reoperations, complications, results, and other topics will be discussed in subsequent publications.

Preoperative Care

The management of the patient prior to operation may be considered as twofold. The first aspect involves a general medical evaluation, which is especially important since general anesthesia is often employed for this type of surgery. Laboratory studies include complete blood cell count, urinalysis, and x-ray examination of the chest. Any medical disorders found are evaluated, and, if necessary, treatment is instituted prior to eye surgery.

The second aspect is the ocular examination, which includes a history of the present illness as well as of any previous ocular disease and the measurement of visual acuity, field of vision, and tension of both eyes. Slit-lamp examination of the anterior segment is performed, and the deep vitreous is studied with the aid of either a highly concave precorneal lens or a contact lens having a flat or slightly convex anterior surface. The most important portion of the examination is the careful and accurate study of the fundus of the eye by means of an indirect stereoscopic ophthalmoscope.[5] Scleral depression is indispensable to an adequate study of the fundus periphery, where retinal breaks are often located. Ophthalmoscopic findings are recorded on a special chart, which is used at the time of the operation for orientation purposes. The chart accurately shows the location of the breaks in relation to easily seen landmarks such as retinal vessels, hemorrhages, and fixed retinal folds; thus, at operation the retinal breaks can be quickly and accurately localized. It is essential to note that the preoperative fundus investigation performed prior to any scleral buckling must be as careful and painstaking as the fundus examination preceding a retinopexy.

Preoperative medication includes antibiotic drops, for example, a mixture of neomycin

0.25% and polymixin B 0.05%, and mydriatics, such as a mixture of 10% phenylephrine hydrochloride and 0.3% scopolamine hydrobromide. Cocaine drops and any kind of ointment are not to be used, since these tend to make ophthalmoscopy difficult; if surface anesthesia is necessary, 0.5% tetracaine drops may be used with caution, as they cause less damage to the corneal epithelium than cocaine. Agitated patients may be made more comfortable and relaxed with phenobarbital, 15 mg. three times a day, or meprobamate, 400 mg. three times a day. In cases complicated by glaucoma, either in the affected or in the fellow eye, 125 to 250 mg. of acetazolamide is usually given by mouth four times a day when the pupil must be dilated. When active uveitis is present, and the process is moderate or severe, systemic corticotropin (ACTH) or steroid therapy may be given preoperatively. Corticotropin is given intravenously, 25 to 40 mg. being diluted in 500 cc. of a solution of 5% dextrose in purified water and administered over a period of six to eight hours. Prednisone may be given by mouth in doses of 10 mg. three to four times per day.

Preoperative bed rest with both eyes covered is used only when an attached macula is threatened by an encroaching detachment or in patients with severe recent vitreous hemorrhage, where bed rest allows settling of the blood so that ophthalmoscopy may be more satisfactory. In all other cases, the patients are encouraged to be up and about, in order to keep the retina detached prior to surgery, because the scleral buckling operation, which necessarily decreases the volume of the eye, requires the loss of ample subretinal fluid at the time of operation. Pinhole glasses are not used either before or after surgery. In most cases only two days' hospitalization is required prior to operation in order to complete the general medical and ophthalmic examination. Two hours before operation the patient is given 150 mg. of pentobarbital by mouth if he is under 55 years of age; chloral hydrate, 1.0 to 1.5 gm., is substituted for pentobarbital in older patients. One hour before operation 50 mg. of meperidine and 0.5 mg. of atropine sulfate are administered subcutaneously.

Surgical Techniques

A scleral buckling operation is nearly always performed under general anesthesia. Thiopental sodium is given intravenously, and an endotracheal tube is used in order to control breathing of a mixture of oxygen and nitrous oxide. A canthotomy is performed, and lid sutures are passed in the tarsal plates near the lid margins for better exposure. The conjunctival incision is made as extensive as is necessary, a complete peritomy being sometimes required. Extraocular muscles are detached whenever indicated; in many cases three recti are severed, and sometimes, four. Special instruments used for scleral buckling surgery are as follows:

Indirect stereoscopic ophthalmoscope and scleral depressor * are indispensable for adequate preoperative work-up; the same ophthalmoscope is used for fundus observation during surgery and for postoperative follow-up.

Desmarres scarifier,† size of blade 4 mm. long and 2 mm. wide, is used for excision of the scleral lamella (Fig. 1*A*).

Sharp cutting spatula,† 1.5 mm. wide, is used for incising the sclera very posteriorly when it is impossible to do this with the Desmarres scarifier (Fig. 1*B*).

Arruga retractor is used for exposing the sclera at the time of localization of the retinal breaks under ophthalmoscopic control.

Forked retractor replaces the Arruga retractor for the other steps of the operation; the slot in its middle permits easier rotation of the suture needle when the mattress sutures are posteriorly located (Fig. 1*C*).

* Manufactured by the American Optical Company.

† Made by Grieshaber, Schaffhausen, Switzerland.

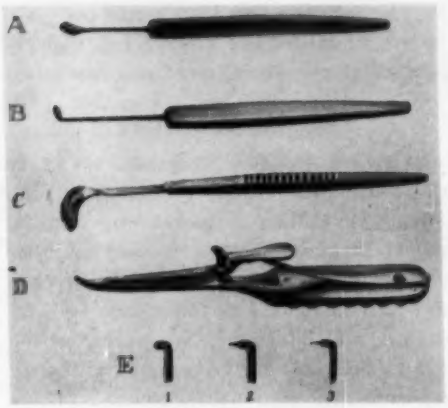


Fig. 1.—Some of the special instruments used for scleral buckling surgery. *A*, Desmarres scarifier (Grieshaber Catalog No. 33/4); *B*, sharp cutting spatula (Grieshaber Catalog No. 125); *C*, forked retractor; *D*, special curved needle holder (Grieshaber); *E*, three electrodes: (*1*) flat tip, for localizing retinal breaks under ophthalmoscopic control; (*2*) blunt point, for applying surface diathermy; (*3*) fine needle, for perforating the choroid.

Polyethylene sheet, thickness 0.0015 in., 50 mm. square,§ is used to repair choroidal hernias and perforations.[8]

Three short lengths of polyethylene tube ‖ are used for short buckles; PE-90, which has an outside diameter of 1.27 mm.; PE-190, which has an outside diameter of 1.70 mm., and PE-205, which has an outside diameter of 2.08 mm.

Polyethylene tube, PE-90, 150 mm. long, with 00 braided black nonabsorbable surgical (silk) suture in its lumen, is used as circling tube.

Black silk sutures, 0000 braided, mounted on Grieshaber needles Nos. 82/7 and 82/5, are used for the mattress sutures.

Special needle holders ¶ (one straight and one curved) with narrow jaws are very useful for handling the small needles, particularly when exposure is poor (Fig. 1*D*).

Amsler marker is used to measure distances from the limbus.

Curved fine-pointed scissors are particularly useful in reoperations.[8]

§ Supplied by Clay-Adams, Inc., 141 E. 25th St., New York.

‖ Clay-Adams, Inc.

¶ Grieshaber.

Electrodes for diathermy applications: flat tip, 1 mm. in diameter, for localizing retinal breaks; blunt needle, 2 mm. long, for applying surface diathermy; fine needle, 2 mm. long, for perforating the choroid (Fig. 1*E*).

Before describing technical details of the operation, it is important to make three general remarks. The first concerns the diathermy applications, which, in our procedures, are practically always made in the bed of the lamellar scleral resection. It has been found advantageous and less traumatic to make light applications with a small applicator, such as a 2 mm. long blunt diathermy point, which is used as a surface electrode; in other words, the blunt point is applied gently and rather tangentially against the thinned sclera, without perforating it (Fig. 2*C*).

The second remark concerns the artificial glaucoma which often occurs during the course of a scleral buckling. When the buckling sutures are drawn and tied, the intraocular tension should be tested at frequent intervals by applying a squint hook on the cornea. If the pressure rises markedly, it is essential that the optic disc be observed to check on the possible existence of retinal ischemia as a result of raised intraocular pressure. With very high pressure the disc appears white and no retinal vessels are seen at the disc. As the pressure is lowered, the arterioles begin to beat; however, the duration that the arterioles remain open is shorter than the time they are closed. As the pressure is lowered still further, the reverse situation is observed in the arterioles, and they remain open longer than closed. We feel that the intraocular pressure at this point probably does not damage the retina or its vessels, since the ischemia has been relieved.

There are three methods for lowering the intraocular pressure, after all available subretinal fluid has been released. First, the buckling sutures may be loosened; second, an intravenous injection of 250 to 500 mg. of acetazolamide may be given, and its effect

is generally noted within five minutes; third, a very careful paracentesis may be performed, provided one fully realizes that this procedure may lead to serious complications. It is probably inadvisable to perform a paracentesis and thereafter tighten the sutures to the point where the pressure again rises markedly. In the latter case the anterior chamber may be flat enough to make a second paracentesis extremely difficult, and an injection of acetazolamide may lead to an undesirably prolonged flattening of the anterior chamber, with resulting peripheral anterior synechiae and closed-angle glaucoma.

The third remark refers to ophthalmoscopic examination during surgery. As this examination is an essential part of our procedures, it is of prime importance to maintain the pupil dilated and the cornea clear during the whole operation. Even though the pupil is fully dilated when the surgery is started, it often contracts later, probably owing to rapid changes in the intraocular pressure; this difficulty may be partly obviated by making a subconjunctival injection of 0.2 cc. of mydriatic solution,# at the start of the operation.[6] In order to maintain the cornea transparent, it is important to moisten it at regular intervals with a saline solution. Artificial glaucoma causes epithelial edema, but the corneal transparency may be restored either with one drop of pure sterile glycerin or by gently scraping off the corneal epithelium with a knife.

The surgical techniques to be described are scleral buckling with circling polyethylene tube, scleral buckling with partial polyethylene tube, scleral buckling without scleral excision, and scleral buckling with a trapdoor flap in the sclera.

Scleral Buckling with Circling Polyethylene Tube.—Technique: After the sclera is exposed, the lid speculum is removed to allow insertion of the Arruga retractor. The surgeon now examines the fundus with an indirect ophthalmoscope while the assistant gently presses the flat-tip electrode against the sclera. With some practice, the rounded elevation of the choroid produced by the electrode is readily seen, even when the retina is highly detached; when this elevation coincides with the posterior edge of a retinal break, the surgeon directs the current to be turned on. This produces a gray mark on the sclera and usually a white burn in the retina; of course, if the retina is markedly elevated no mark will show in the fundus. All significant retinal breaks are localized in this fashion, with great care being taken not to damage a vortex vein; the diathermy marks on the sclera indicate the position of the breaks. The distance of these marks from the limbus is measured with an Amsler marker so that the location of the buckle may be determined; only the posteriorly located retinal breaks are considered in determining this location. For example, if there are four breaks in the temporal half of the retina, the posterior edges of which are located 10, 12, 13, and 14 mm. from the limbus, the resection is done 13 to 16 mm. from the limbus, 3 mm. being the usual width (Fig. 2*A* and *B*). If all breaks are in the vicinity of the ora serrata, there are at least three reasons why it is generally preferable to place the resection at the equator rather than more anteriorly. First, an equatorial fixed fold often forms, even postoperatively, and an equatorial buckle is the best method to combat the ill effects of this type of fixed fold; second, the thinness of the sclera close to the attachment of the recti muscles often makes an anteriorly located buckle technically difficult, and, third, a buckle which is too anterior has a tendency to slip forward, with some loss of the buckling effect.

If the breaks in one quadrant are very posteriorly located, the scleral excision in this area should be placed over them. In order to prevent the circling tube from slipping posteriorly, it is necessary to bring it anterior to the equator in the quadrant opposite to that of the posterior breaks; in

Phenylephrine hydrochloride, 5 mg.; homatropine hydrobromide, 4 mg.; procaine hydrochloride, 10 mg., and purified water, 1 cc.

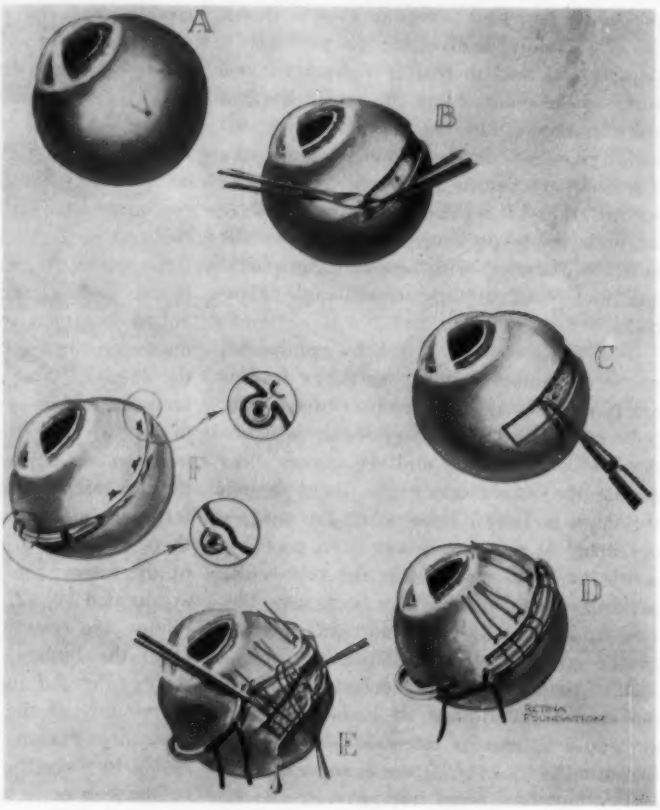


Fig. 2.—Scleral buckling with circling polyethylene tube. *A*, a diathermy mark is made, under ophthalmoscopic control and with a flat-tip electrode, on the posterior border of two retinal breaks. The latter are outlined on the sclera with dotted lines. *B*, a scleral lamella is excised, parallel to the equator; the localizing diathermy marks are placed halfway across the width of the excised strip of sclera. *C*, surface diathermy is applied to the area of scleral excision, with a blunt diathermy point used in a somewhat tangential fashion. Note that the end of the excised area is not tapered. *D*, Mattress sutures are placed as indicated; a circling polyethylene tube is introduced under the sutures and cut to fit around the eye; the circling suture is drawn up and locked. *E*, the circling tube is gently pulled to the side; the sclera is incised in a meridional direction, and a fine diathermy needle is used to perforate the knuckle of choroid. It is preferable to perforate under a mattress suture. *F*, all sutures are drawn up and tied. The cross section above shows the buckle in the area of scleral excision; the cross section below shows the smaller indentation caused by the circling tube where no sclera was excised.

other words, the circling tube should, as far as possible, course approximately along a great circle of the eyeball.

The scleral incisions are made with a Desmarres scarifier by scratching down on the sclera and spreading the cut edges until a bluish color is seen. When the sclera between the two incisions is resected, it is important that the remaining layer of sclera, which is one-quarter to one-half of its thickness, be as uniformly thin as possible; the reason for this will become evident in the following section. One-half to three-quarters of the circumference of the globe is usually resected. It should be remembered that grasping the cut edge of the sclera with toothed forceps causes scleral edema postoperatively, and mattress sutures readily cut through the edematous sclera; consequently, only the scleral lamella should be grasped with the forceps.

As each quadrant is resected, light diathermy is applied to the uniformly thinned sclera with a blunt needle electrode, as described above (Fig. 2*C*). One or two 0000 black silk mattress sutures are placed across the resected quadrant. A single knot is tied so that the suture may be pulled up quickly

and locked if necessary. These sutures need not be placed closer than 8 to 10 mm. from each other except when the sclera is thin everywhere; in the latter case it is advisable to use more sutures. The ends of the resection are not tapered (Fig. 2*D*), and this is contrary to the practice in a classical scleral resection.

It is safer to resect the sclera, treat it with diathermy, and suture it in one quadrant at a time. When the entire length of the buckle is completed in this fashion, the mattress sutures are loosened and a circling tube, which was described earlier, is passed under them and under any muscles not detached. The polyethylene tube is then cut to fit exactly around the globe and the 00 black silk suture which is in the lumen of the tube is drawn up and locked. A short scleral incision is made by scratching, generally in a meridional direction, in the resected area, usually where subretinal fluid is most abundant, but not over the location of a retinal break (Fig. 2*E*). Whenever possible, it is advisable to make the scratch incision under a mattress suture because, in case of vitreous loss, tying the suture will press the tube against the perforation and close it hermetically. The incision should be carried through the sclera, at which point a small knuckle of choroid will be seen between the lips of the incision. If, after careful inspection, no large choroidal vessels can be seen in the knuckle of choroid, it is perforated with the fine 2 mm. needle electrode, held tangentially to the globe. Extreme care should be taken not to perforate large choroidal vessels; the vortex ampullae and the long posterior ciliary arteries are particularly to be avoided. It is generally safe to perforate either under the inferior or under the superior rectus muscle, between the lateral and the medial vortex vein. A tiny perforation is all that is necessary, as a large perforation causes a sudden gush of fluid and may lead to intraocular hemorrhage, incarceration of the retina into the perforation, and vitreous loss; multiple perforations are seldom indicated. As the globe becomes soft with the release of subretinal fluid, the mattress sutures are gradually drawn up; tying the single knots usually locks the sutures. If the eye is very soft after all the mattress sutures are drawn up, it is necessary to pull up the suture which is in the circling tube so that the intraocular pressure reaches a low normal level. In order that this may be done, the circling tube usually must be shortened; in cases of massive vitreous retraction this shortening averages 25 to 35 mm.

The fundus is examined to ensure that the retinal breaks lie either on the anterior slope of the buckle or further anteriorly; if a break is partly or completely located on the slope of the buckle which is on the side of the disc, this defect must be corrected, and methods of correction are described elsewhere.[8] When the ophthalmoscopic examination shows that subretinal fluid is still present, especially over the buckle, the single knots are loosened and additional fluid is released either through the original perforation or through a second perforation, made in the area where most of the fluid is found. After this, the sutures are again drawn up, and the fundus is reexamined. Ideally, the retina should be in contact with the buckle everywhere, and this is actually the case in a large number of instances. The mattress sutures may now be tied permanently, the intraocular pressure being checked from time to time and the pressure being maintained within reasonable limits by the methods described earlier (Fig. 2*F*).

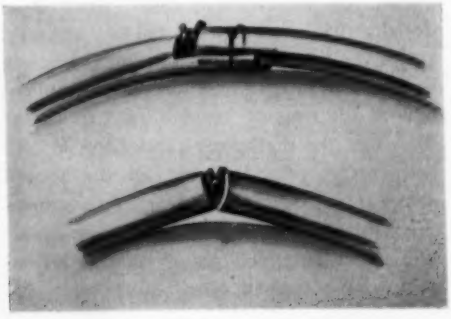
As a rule, no diathermy is applied to connect the area of the resection with the ora serrata. In unfavorable cases, when it is probable that a reoperation will be necessary, such a diathermy connection would weaken the sclera and might lead to severe complications at the time of reoperation. In favorable cases the diathermy connection is also unnecessary, provided that all the retinal breaks are on the buckle. The only instances where this connection is indicated are favorable cases in which some of the retinal breaks are still open, being located anterior

to the scleral buckling. When a diathermy connection has to be made, it should be done before the mattress sutures at each end of the buckle have their second knot tied. If the eye is very soft, the intraocular pressure should be raised before the additional diathermy is applied; this is accomplished by drawing up the circling suture. Two or three rows of partially penetrating diathermy are then applied from each end of the buckle to the ora serrata, located about 6 mm. from the limbus. This additional diathermy walls off the region anterior to the buckle from the remainder of the retina.

One end of the polyethylene tube is split in two for a distance of 3 mm., and the half away from the globe is cut so that the other end overrides the split end (Fig. 3). The 00 suture which passes through the lumen of the tube is then tied, and an additional suture is passed through the overriding ends of the tube. It is essential not to increase the intraocular pressure excessively when the final knots are made in the circling suture.

The muscles are recessed about 2 mm. when they are reattached; the medial rectus is usually not recessed. A running plain absorbable surgical (gut) suture is used to close the conjunctiva, with locking bites in each quadrant; the canthotomy is also sutured. Four per cent atropine is instilled, and 200,000 units of penicillin in 1 cc. of saline are injected subconjunctivally in the vicinity of the scleral sutures; no ointment is used, since this would interfere with fundus examination on the following day. A pressure dressing of elastic adhesive bandage (Elastoplast) is finally applied.

Fig. 3.—Scleral buckling with circling polyethylene tube. Above: Correct method for tying the 00 silk circling suture; one end of the polyethylene tube is split in two, and the half away from the globe is cut so that the other extremity of the tube overrides the split end; an additional suture is passed through the overriding ends of the tube. The circling tube fits the eyeball properly. Below: Incorrect method for tying the 00 silk circling suture; the circling tube fits the eyeball poorly in the area of the knot.



Indications: The scleral buckling operation with a circling tube is used in the majority of our cases, whenever enough fluid can be released to make it possible to draw up the mattress sutures and tie the circling tube. It is especially useful in detachments with large breaks, with multiple breaks, or with fixed folds; detachments with aphakia or with high myopia also do well with this procedure. In our hands it is the only operation to which cases of massive vitreous retraction have responded. This procedure was at first reserved for very unfavorable cases, and reattachments were obtained in patients who were considered incurable by any operation tried hitherto. The reason for such successes lies probably in the fact that this is the only procedure, known to us, by which a permanent and extensive choroidal elevation, reaching a height of 6 mm. and even more, can be safely obtained in the area treated with diathermy. As experience with this procedure increased, it was used on more and more favorable cases, and it was found to be the most dependable operation, so that if sufficient subretinal fluid is available the circling tube is now used routinely.

Scleral Buckling with Partial Polyethylene Tube.—Technique: This procedure, which antedates the circling tube operation, is identical to the latter operation except for the absence of a suture in the lumen of the tube and for the length of the polyethylene tube, which may vary from 5 mm. to three-quarters of the circumference of the globe. Exposure of the sclera, localization of the breaks, resection of the sclera, and application of diathermy are carried out in the manner described previously. The mattress sutures across the resected area should,

however, be placed more closely together, since these sutures alone support the polyethylene tube, without the help of a 00 silk suture in the lumen of the tube, as in the circling tube operation. Before the subretinal fluid is released, diathermy is generally applied from each end of the buckle to the ora serrata.

If a tube shorter in length than half the circumference of the globe is used, it should be anchored to the sclera in order to prevent its migration. In all cases it is important to bury the two ends of the tube as well as possible in the bed of the resection; this is best accomplished by using a tube a few millimeters shorter than the length of the scleral resection and by tapering the ends of the resection. In nearly all cases, a partial tube should be of small diameter (PE-90), which helps to prevent migration. If a tube of larger diameter is used, it should, as a rule, not be longer than about 8 mm.; a very posteriorly located partial tube is always short. The direction of the tube is not necessarily parallel to the equator; it may be meridional or oblique, depending on the shape and position of the retinal break to be sealed.

Indications: A partial polyethylene tube is used when there is insufficient subretinal fluid for use of a complete circling tube. Very often a circling polyethylene tube is placed under the mattress sutures, and if, after perforation of the choroid, only a small amount of fluid can be released, the circling tube is cut and the circling suture is removed, only that part of the tube being used which is under the mattress sutures. Although the partial tube operation is effective in many cases, the buckle cannot be made as high and as permanent as in the circling tube operation. In unfavorable cases, reattach-

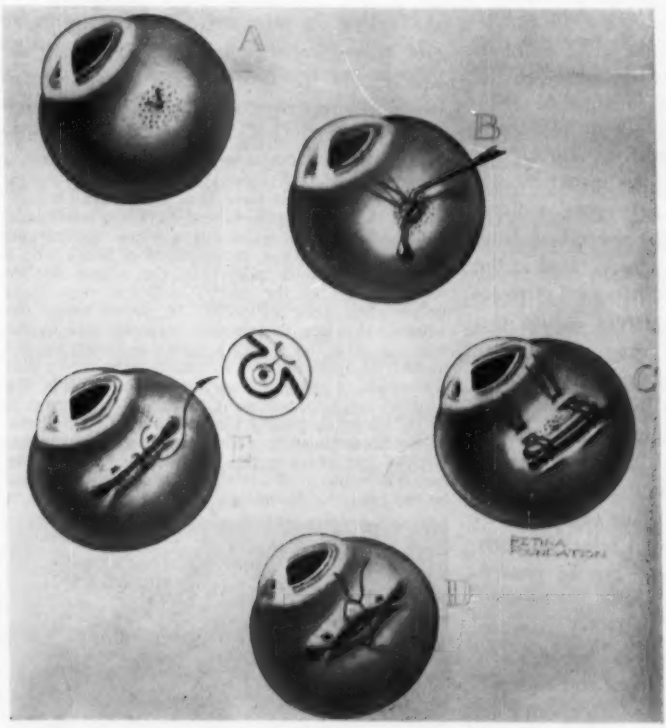


Fig. 4.—Scleral buckling without excision, on a case showing one small break and a limited retinal detachment. *A*, the localizing mark is surrounded by several rows of light diathermy. *B*, a scleral incision is made; a mattress suture is placed on the lips of the incision, and the knuckle of choroid is perforated with a fine diathermy needle. After the subretinal fluid has escaped, the mattress suture is drawn up and locked. *C*, two additional mattress sutures are placed in untreated sclera, and a short polyethylene tube is passed under them. *D*, the mattress sutures are drawn up and locked, and the fundus is checked; if the retina is reapplied against the choroid in the buckled area, all mattress sutures are tied. An anchoring suture is passed through the sclera and the tube, to prevent the migration of the latter. *E*, Partially penetrating diathermy is applied to connect each end of the buckle with the ora serrata; the insert shows a cross section of the buckled area.

ments are less frequently obtained with this procedure.

When a retinal break cannot be easily reached with a circling tube, a short partial tube may be indicated: This may occur when the orbit is small and a retinal break is located more than 20 mm. from the limbus.

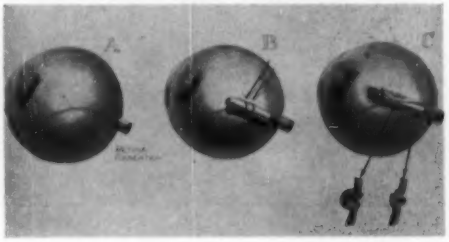
Scleral Buckling Without Excision.—Technique: This somewhat simpler procedure is also called retinopexy with implantation of polyethylene tube (Fig. 4). After the sclera is exposed, the posterior edge of the retinal break is localized under ophthalmoscopic control; in case of a small break, the localizing mark may cover it entirely. With use of this mark as a guide, the area is surrounded with one to three rows of diathermy applications, depending on the size of the break; for this purpose, we favor the use of either partially penetrating diathermy or surface diathermy with a blunt needle (Fig. 4*A*).

A scratch incision 2 to 3 mm. long is then made in the treated sclera; before the choroid is reached a mattress suture is placed on the lips of the scleral incision (Fig. 4*B*). Once the mattress suture is in place, the incision is continued until a knuckle of choroid is seen. This is perforated by use of a needle electrode in a tangential direction, in order to release the subretinal fluid. Should the retina become incarcerated in the choroidal opening, or should formed vitreous be lost, the preplaced mattress suture can be drawn up and tied. If very little subretinal fluid escapes and ophthalmoscopy shows that the retina has flattened out adequately, no scleral buckling is performed. If enough subretinal fluid is lost to permit a buckling, the mattress suture is pulled up and locked. One or two other mattress sutures are placed in untreated sclera in such a fashion that a short tube can be passed under them (Fig. 4*C*); the tube is generally of fairly large diameter (PE-190), because it is short. When the mattress sutures are pulled up they elevate the sclera and choroid in the region of the break, which should lie on the anterior slope of the buckle. As a rule, the tube is placed parallel to the equator, but it may be placed in any direction, as in the case of the scleral buckling with short partial polyethylene tube.

The fundus is examined; if there is no residual fluid under the retina, the sutures are tied, and one or two anchoring sutures are placed through the tube and sclera (Fig. 4*D*). When the retinal break is large, a double row of partially penetrating diathermy is applied from each end of the buckle to the ora serrata in order to wall off the area of the break (Fig. 4*E*).

In treating macular breaks with this procedure, a few modifications are necessary (Fig. 5). The lateral rectus, inferior rectus, and inferior oblique muscles are temporarily detached, and the macula is localized under ophthalmoscopic control with the flat-tip electrode. If the macular break is about the size of the disc or larger, one or two additional surface applications may be necessary (Fig. 5*A*). It should be remembered that the sclera in this area is generally thick and, therefore, that it is necessary to make a relatively strong diathermy application in order to affect the choroid. If the subretinal

Fig. 5.—Buckling without excision for a macular break. *A*, lateral rectus, inferior rectus, and inferior oblique have been temporarily tenotomized. A localizing diathermy mark has been made, followed by two additional surface applications aimed at covering a large macular break. *B*, a mattress suture is placed in the sclera on the temporal side of the macula, and a medium-sized polyethylene tube (PE-190) is passed under the suture. *C*, after the choroid is perforated in the macular area, the mattress suture is drawn up and locked; if ophthalmoscopic examination shows that the retina is reapplied against the choroid in the buckled area, the suture is tied and, in addition, a single suture is passed through the sclera and the polyethylene tube in order to prevent migration. On the left, cross section of the buckle under the mattress suture; on the right, cross section of the buckle over the macular break.



fluid is limited to the area of the posterior pole, the sclera is not incised, and a single perforating diathermy application is made with a fine needle over the macular break in order to release the subretinal fluid. A tube 8 to 10 mm. long, size PE-190, is placed horizontally across the macula, under a single mattress suture (Fig. 5*B*). The temporal end of the tube is anchored to the sclera (Fig. 5*C*). When exposure of the posterior pole is relatively easy, it is preferable to place the mattress suture in the sclera before releasing the subretinal fluid. If exposure is poor, the mattress suture should be placed after perforation of the globe, because this improves exposure.

When considerable subretinal fluid is present in the inferior half of the fundus, a perforation is made at the point where subretinal fluid is most abundant. In this case, however, it is important first to place the mattress suture which will hold the polyethylene tube over the macula, because perforation may make the eye so soft that suturing of the sclera would be difficult. Release of subretinal fluid is done through a scratch incision in the sclera; a mattress suture is placed on the lips of the scleral incision, and diathermy is applied with a blunt needle to the bottom of the scratch incision. A knuckle of choroid is then exposed and perforated, as previously described.

A word of caution may be interposed here, as macular breaks are extremely rare and many instances of macular cyst are mistakenly diagnosed as macular breaks. If any other retinal breaks are present, they should be treated first and the macular area should be left alone. Should this prove unsuccessful, and should the macula still look very suspicious, the above procedure may be used as a second operation. The method described for the treatment of a macular break is of course applicable to any break located very posteriorly.

Indications: A first indication is the case of a retinopexy where perforating of the choroid releases an unexpectedly large amount of subretinal fluid. Such occurrence may be observed when there is a moderate-sized retinal break, through which fluid vitreous passes and escapes through the choroidal perforation. In this type of case, it is often seen that even a substantial loss of fluid does not flatten the retina against the choroid. This unfortunate situation is adequately corrected by simple implantation of a short polyethylene tube.

Another indication for this procedure is a retinal break which is located so posteriorly that the sclera over the break is not easily accessible for lamellar excision; macular breaks fall in this category.

Scleral Buckling with a Trap-Door Flap in the Sclera.—Technique: The sclera is exposed in the usual manner, and the posterior edge of the break is localized (Fig. 6*A*). The sclera is incised as for an ordinary scleral buckling, but the surgeon omits either the anterior or the posterior incision, so that a hinged flap of sclera remains attached to the globe (Fig. 6*B*). The flap should be of such a size that it covers more than the area occupied by the retinal break, and the localizing mark should be approximately in the center of the resected area. Surface diathermy is applied with a blunt needle electrode to the area from which the scleral flap was dissected (Fig. 6*C*). Since the retina is generally not detached in cases where this procedure is used, diathermy should be just strong enough to show a small white mark in the retina; a stronger application may result in burning a hole through this membrane. One or two mattress sutures are placed across the resected area, and a polyethylene tube just long enough to fit into the resected area, and generally of large diameter (PE-190 or PE-205), is placed under the sutures (Fig. 6*D*). As there is little or no subretinal fluid, a choroidal perforation is generally not performed; when indicated, the perforation is often done in the resected area and according to the method already described. Before the mattress sutures are tied, the flap of sclera is replaced over the

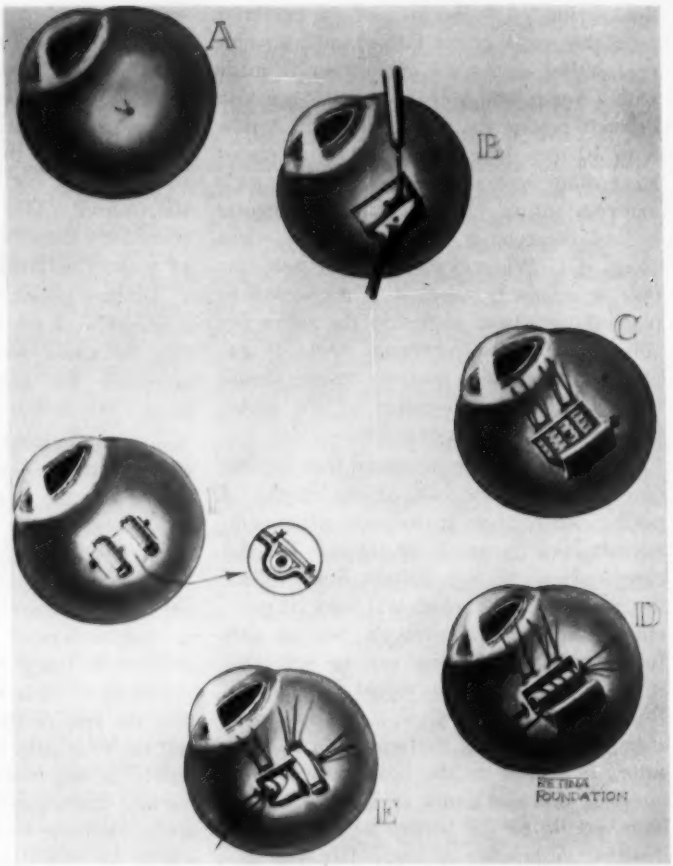


Fig. 6.—Scleral buckling with a trap-door flap in the sclera. *A*, a diathermy mark is placed on the posterior edge of the retinal break. *B*, a trap-door flap of sclera is dissected. *C*, light surface diathermy is applied to the resected area, and two mattress sutures are placed as shown. When no subretinal fluid is present, no perforation of the choroid is made; if a perforation is necessary, it is generally performed in the resected area. *D*, a tube of polyethylene, cut to fit exactly under the trap door, is placed under the sutures. The mattress sutures are drawn up and locked and the fundus appearance is checked; if the tube is in the correct position, it is anchored in position with a single suture at each end. *E*, a polyethylene plate is placed under the loops of one mattress suture; the same is done for the second suture. *F*, completed operation, showing the four sutures tied, with a polyethylene plate under each mattress suture. Insert shows a cross section of the buckle obtained with this procedure. The length of a trap door rarely exceeds 10 mm.

tube; a polyethylene "plate" is then passed under the two loops of each mattress suture (Fig. 6*E* and *F*). This plate consists of a polyethylene tube which is split lengthwise; a small notch is cut at one end of the half-tube. The plates prevent the sutures from cutting through the sclera and hold the scleral flap securely in place. In addition, two or more single sutures may be used to approximate the cut edges of the sclera. It is sometimes necessary to anchor the ends of the tube to the sclera, since it is usually not longer than 8 mm. As in the partial tube operation, a diathermy connection is often made from each end of the buckle to the pars plana region. Several individual trap doors may be made over several widely separated retinal breaks. The trap-door flap and its polyethylene tube are generally parallel to the equator; however, they may be oriented in a meridional or oblique direction, depending on the shape of the retinal break to be covered.

Indications: This operation is mainly used in case of a retinal break with only a minimal amount of detachment. It makes the chorioretinal adhesion, in the treated area, more certain, because the diathermy applications are placed over uniformly thinned sclera; by the same token, it permits the use of very weak diathermy applications and considerably reduces the risk of postoperative complications, particularly vitreous hemorrhage. It also avoids the risk of creating an exudative detachment in the treated area, which may change the preexisting sub-

clinical detachment into a fully developed clinical detachment. Finally, it allows ambulation on the first postoperative day and leads to quicker recovery.

Another indication for the trap-door flap in the sclera is a single retinal break of fairly small size and posteriorly situated; in this case the trap door may be used in addition to either a partial or a circling polyethylene tube, located more anteriorly.

Postoperative Care

After operation there is a variable degree of ocular discomfort, and drugs, such as a subcutaneous injection of meperidine, 50 mg. every four hours, if necessary, are given during the first few days. Later, many patients experience a variable degree of referred pain in the distribution of the ophthalmic branch of the fifth nerve; this can usually be controlled by salicylates. Postoperative nausea and vomiting respond well to chlorpromazine, 25 mg. being given either intramuscularly or by mouth, repeated as often as four times a day for one or two days, if necessary. Since retina operations necessarily are longer than most ocular procedures, the chances of infection are increased; for this reason, antibiotics, such as procaine penicillin, given intramuscularly, 300,000 units twice a day, or erythromycin by mouth, 250 mg. every six hours, are used for three to four days postoperatively. While in bed, the patient is placed in any position which is found comfortable and is permitted to change position whenever he wishes.

The eye is examined on the first postoperative day; the anterior segment is inspected, and generally it is possible to evaluate the fundus appearance with the indirect stereoscopic ophthalmoscope. Local medication is instituted and consists of mydriatic drops four to eight times a day; usually a mixture of scopolamine hydrobromide 0.3% and phenylephrine hydrochloride 10% is used. In addition, it has been found that 0.5% cortisone acetate drops, four to eight times a day, decreases the incidence and severity of postoperative anterior uveitis and posterior synechia formation. Antibiotic drops are occasionally prescribed, especially if there is an abnormal amount of secretion; ointments are not used, since these interfere with fundus examination. Systemic acetazolamide and steroids may be continued postoperatively if indicated.

If the fundus can be evaluated on the first postoperative day and the breaks are anterior to or on the buckle, the patient is allowed to have the fellow eye open and to use his regular corrective lens; a single eye pad is placed on the eye operated on for the next three or four days. In addition, the patient is allowed to be up and is encouraged to walk. This early ambulation has proved of great value in decreasing the incidence of phlebothrombosis and possible pulmonary infarction. It is well to prohibit prolonged sitting, since this increases venous stasis in leg veins.

In the event that the break is not anterior to the buckle and, in addition, is not in contact with the buckle, the management varies. When the break is in the upper half of the fundus, elevation of the patient's head may result in a downward movement of the subretinal fluid, which brings the break in contact with the buckle; it may be advisable for such patients to keep both eyes covered for a day or two until this occurs. When the break is in the lower half of the fundus and is not in contact with the buckle, rest in bed with both eyes covered may be advisable for a few days until contact is established between the break and the buckle.

After five to seven days the patient is usually ready to leave the hospital; mydriatic and cortisone acetate drops are continued three to four times a day. Activity at home includes walking, bending over, use of stairs, televiewing, shaving, brushing of teeth, and combing of hair. Unnecessary automobile trips and manual work should be avoided, and prolonged reading is usually uncomfortable.

Postoperative examinations are made at the office at increasing intervals of time, the first visit being about one week after dis-

charge from the hospital. It is necessary to continue mydriatics and local cortisone therapy until the anterior uveitis which follows retina surgery has cleared, this period usually being four to six weeks. Patients who have sedentary vocations may return to work three to six weeks after operation; those doing heavy manual labor are advised to return to work after two to three months.

Conclusions

The scleral buckling operations are designed to push the diathermized choroid into contact with the retina, thereby directly and permanently sealing or walling off the retinal breaks. Shortening of the sclera or choroid is definitely not the primary aim of these operations. In our experience scleral bucklings create a higher and more permanent ridge in the fundus than any other procedure. Therefore, they are considered the most efficient operations for slackening traction exerted on the treated area of the retina, for instance, in cases where vitreous traction holds the retina in a detached position.

The scleral bucklings have greatly shortened the hospital stay of the average retina patient. Whereas with retinopexy procedures the average hospital stay was 26 days, with scleral bucklings it has been reduced to 7 or 10 days. Moreover, the omission of bed rest before operation and early ambulation postoperatively has reduced complications such as phlebothrombosis, pulmonary infarction, urinary retention, general weakness, anorexia, and mental depression. Finally, patients on whom a scleral buckling operation is performed do not need pinhole glasses at any time and return to work much sooner.

Another advantage of scleral bucklings concerns reoperations. After diathermy has been applied, as it is in a retinopexy or in a classical scleral resection, the sclera becomes weak and prone to rupture when a reoperation is performed; this is especially true of eyes which had a thin sclera originally. In the scleral buckling procedures the diathermized, weakened sclera is buried, which diminishes the adhesions to Tenon's capsule and minimizes the risk of accidental globe perforation at reoperation.

It is often said that scleral buckling procedures are more traumatic than either retinopexy or simple lamellar scleral resection; three facts should be kept in mind in this respect. First, the most traumatic operation is that which destroys the largest area of choroidal and retinal tissue, for instance, with unnecessarily heavy or extensive diathermy applications. In scleral buckling procedures diathermy applications are generally restriced to the area of the scleral resection and are of low intensity, because they are applied to an evenly thinned sclera. In retinopexy the diathermy is applied over intact sclera, and this is also the case for much of the diathermy used with the classical type of lamellar scleral resection. Such diathermy must necessarily be heavier to be effective; in addition, it generally covers a larger area than in scleral bucklings, resulting in severer trauma to the choroid and retina. The second fact to consider is that in scleral bucklings the sclera is admittedly more traumatized than in other procedures, but this is a far less essential tissue than either choroid or retina, as repair processes in the sclera do not interfere with visual functions. Third, experience has shown that, in spite of the scleral trauma inflicted by scleral buckling procedures, reoperations are considerably easier and better tolerated after scleral bucklings than after other procedures.

In our hands, scleral buckling procedures have improved the percentage of reattachments over that obtained by retinopexy and other procedures. In 1953, Smith and Pierce [9] reported successful results in 70% of our cases after retinopexy, with a six months' follow-up period. Preliminary sampling of our present records shows that the scleral buckling operations have raised this figure in spite of the fact that many patients who are now being operated upon successfully were previously considered to have inoperable conditions; cases of this type were obviously excluded from statistics related to retinopexy.

Summary

A scleral buckling operation consists essentially in closing or walling off the retinal breaks with diathermy and then indenting the treated area toward the vitreous cavity, by means of a polyethylene foreign body imbedded in the sclera. The surgical techniques and indications of four basic procedures of scleral buckling are described. These procedures are scleral buckling with circling polyethylene tube, scleral buckling with partial polyethylene tube, scleral buckling without excision, and scleral buckling with a trap-door flap in the sclera. The pre- and postoperative care is discussed, and points differing from the management of a retinopexy are stressed. In conclusion, we find scleral buckling procedures safer and less traumatic than either retinopexy or classical types of lamellar scleral resection. In our hands scleral bucklings yield a larger percentage of reattachments; they permit early ambulation, which avoids a number of postoperative complications, and make reoperations considerably easier than after other procedures.

The illustrations in this article were drawn by William Stenstrom.

327 Charles St. (14).

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Experience of Treating Retinal Venous Occlusion with Anticoagulant and Antisclerosis Therapy

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Occlusion of the central vein of the retina is a serious disease. Opinions on its treatment have continued to differ, and the results achieved are far from always satisfactory. This, notwithstanding the fact that an important etiological factor of the pathogenesis of this disease, viz., arteriosclerosis, has been and still is the subject of lively research.

Anticoagulant therapy was introduced in 1937 for occlusion of the central retinal vein.[10] It proved beneficial.[4,13,17,18,22,24,25] However, anticoagulants, heparin and bishydroxycoumarin (Dicumarol), were found to be incapable of improving the prognosis of the disease as regards either vision or secondary glaucoma.[2]

Material

This is a comparative study of the experience gained at the Ophthalmic Clinic of the University of Helsinki in 1951-1956. The material consists of 81 retinal venous occlusions in 75 unselected patients who consulted the clinic for therapy.

Various therapeutic methods have been tried at our clinic against thrombosis. In 1951, 1954, 1955, and 1956 anticoagulant therapy, or this combined with so-called antisclerosis therapy, was administered to some 10 thrombotic patients per annum and to a total of 35 patients in 37 cases of retinal venous occlusion. In 1952 and 1953, again, a "nihilistic" trend prevailed and the above therapy was tried on only two patients, the remainder usually being referred from the outpatient department to the department of internal medicine. The latter group included also the patients who could not or did not want to be hospitalised for anticoagulant therapy. They constitute the control material, of 41 patients.

The patients were invited to a follow-up examination in 1956. Eight of them, however, failed to appear, despite repeated requests. Six of these eight belonged to the control group, and only two to the group of patients receiving anticoagulants. In addition, five patients of the control group had died. All the patients to whom anticoagulant therapy had been administered were alive, according to the official information received by us. The patients that had died are included in the control material; those who failed to attend for a follow-up are not.

Therapy

We have always endeavoured to begin anticoagulant therapy with heparin, instantaneous in effect. This property recommended it especially in early cases. But, even for early cases, most researchers are of the opinion that heparin has only an anticoagulative effect. Some experimental investigations on fresh thromboses, however, suggest a thrombolytic property in heparin.[9,29] Even in cases treated late there is some hope of promoting recanalization of the thrombus.[16,29]

We aimed at an antiarteriosclerotic effect in the sclerotic cases by prolonged admin-

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istration of heparin in small doses and of vitamins E and A.

According to recent investigations, biologically active heparin occurs in blood normally,[7] and the absence of this endogenic heparin may, several investigators consider, be a reason for the abnormally increased serum lipid values. As a component of lipoprotein lipase, heparin helps to break up lipoproteins in the blood and prevents their accumulation. When the intimal cement substance is swollen it prevents the lipoproteins from entering the intima. If deposition has already taken place, heparin may prove capable of splitting up the lipoproteins in the plaques themselves.[28] On the other hand, a relationship between the absence of heparin-forming heparinocytes and atherosclerosis has been established.[3] During experimental vitamin E therapy the number and size of heparinocytes increased.[1] Hence, the effect of vitamin E might possibly lie in its ability to increase the production of endogenic heparin. According to other investigators, vitamin E, in large dosage, is also an effective anticoagulant.[27] But there are other views on this effect. Vitamin A probably reinforces the effect on vitamin E.

Two programs, short-term and long-term, were applied in the therapy.

Short-term therapy consisted of anticoagulant treatment alone. It was instituted immediately after the patient's admission to hospital, in conjunction with the pertinent medical treatment. The course always commenced with intensive heparin medication intravenously (dosage generally 150, 125, 125, 150 mg). In exceptional cases the heparin was administered intramuscularly or subcutaneously. In addition to heparin, the administration of bishydroxycoumarin or phenindione (Trombosol) was commenced, and heparinization was discontinued when the blood prothrombin had dropped to the desired level. Use was made of the Quick-Lehmann prothrombin test, and the target was 20% to 40% of normal value. This treatment was generally continued for 10 days to 3 weeks.

Long-term therapy (anticoagulant plus so-called antisclerosis therapy). The period of intensive heparinization usually lasted 10 to 14 days. (It was sometimes necessary to administer bishydroxycoumarin for poor veins.)

This was followed by the administration of vitamin E per os, 100 mg. three times a day, or a preparation of vitamins E and A (Rovigon, Roche), 1 tablet three to four times a day. One hundred milligrams of heparin sodium twice a week was given either in addition to vitamins or alternately with them. The treatment was continued for months, even years.

In the following the short-term therapy is denoted briefly as AC-Tr; the long-term, as Comb-Tr.

In addition to anticoagulant therapy, calcium and rutin were usually administered, and often also vasodilative drugs were administered for some periods.

The patients constituting the control material received medical treatment plus, as above, calcium and rutin and sometimes also vasodilator drugs.

Etiology and Pathogenesis

The case reports are given in tabulated form (Appendixes I and II). Table 1 gives a general survey of the factors considered to have etiologic significance for the occlusion of the central retinal vein. The occlusions mostly occurred in persons past middle age. Mild, moderate, or severe hypertension [8] was established in 71% of the cases. Various sclerotic manifestations were diagnosed in the medical examination in 63%, alone or concurrently with hypertension. (Sclerotic changes in the retinal veins of the "other" eye were found in 72%.) Most patients had a cardiovascular affection. Considerably less frequent were other obviously thrombotic-inducing diseases, e. g., diabetes, polycythemia, anemia, glaucoma, and various infections, occurring only in scattered cases either alone or in connection with the above involvements.

TABLE 1.—*Etiological Factors in Retinal Venous Occlusion*

	With AC-Tr,* Comb-Tr (33 Patients)	Without AC-Tr, Comb-Tr (Control Group) (36 Patients)	Total (69 Patients)
Age, Yr.			
≤50	7	8	15
>50	26	28	54
Sex			
Male	14	14	28
Female	19	22	41
Blood pressure			
Hypotension	5	1	6
Normal	5	6	11
Hypertension	22	27	49
No information	1	2	3
Clinical manifestations of			
Arteriosclerosis	21	22	43
Coronary artery disease	9	11	20
Cerebral sclerosis, aortic sclerosis, etc.	13	11	24
Cardiac failure	3	5	8
Other eye retinal arteriosclerosis	26	24	50
Diabetes mellitus	1	3	4
Polycythemia	1	1	2
Anemia	2	--	2
Maxillary sinusitis and other infections	5	4	9
Simple glaucoma	6	1	7

*AC-Tr, anticoagulant treatment; Comb-Tr, anticoagulant and antisclerosis treatment.

Thrombosis occurred also in younger patients, even in seemingly healthy persons. The age group 50 and under comprised 15 persons (22%). Eight of them were found to suffer from the above thrombotic-inducing diseases, and two had extremely low blood pressure. A possible inflammatory etiology was discovered in 3 of these 15 patients.

Of the seemingly healthy persons, five were under and three were over 50.

It will also be seen from Table 1 that both of the groups, the treated (AC-Tr, Comb-Tr) and the control cases, show a fairly even distribution in the etiologic classification. Hence, in this respect, both groups ought to be similar as regards prognosis.

According to Klien's histologic studies, awarded an A. M. A. prize, there are three different types of retinal venous occlusion:

1. Occlusion by compression is caused by the sclerotic central artery or its branches.

2. Primary degenerative or inflammatory disease of the venous wall may also lead to occlusion.

In both cases the occlusion develops gradually, as does loss of vision.

3. In occlusion by stagnation thrombosis, which develops in connection with various hemodynamic disturbances in the retinal circulation at a site where the intraocular pressure exceeds the venous pressure, the loss of vision is sudden.

These different types of occlusion are often concurrent in practice.

In the majority of our patients the sclerotic component had an important role. This was indicated by (*a*) the general sclerotic manifestations, (*b*) the sclerotic changes (in 72%) of the retinal veins of the "other" eye, and (*c*) the slow onset of the disease. However, in many of these cases, too, the final occlusion was caused by stagnation.

Occlusion by stagnation thrombosis occurred in our material in the following conditions: hypertension; cardiac failure; blood diseases; low blood pressure, usually in senility, and glaucoma.

A primary inflammatory etiology was traced in only a few cases of occlusion.

Assessment of Results

In assessing the therapeutic results attention has been paid specifically to vision, defects of the visual field, tension and changes in the fundus.

(1) Good result: vision 1.0-0.6; no, or controlled, secondary glaucoma; (2) fair result: vision 0.5-0.1; no, or controlled, secondary glaucoma; (3) poor result: vision less than 0.1, but good peripheral field; no, or controlled, glaucoma; (4) nil result: vision less than finger counting at 2 meters and no peripheral field, or uncontrolled secondary glaucoma.

To facilitate the comparison of results we have used in part percentages (like other investigators in this field for groups of the same size), although we are well aware of the fact that these figures are not really mathematical evidence.

I. Patients Treated with Anticoagulants (AC-Tr and Comb-Tr) (Appendix I).—In this group, of 33 patients, central vein occlusion (trunk thrombosis) occurred in

TABLE 2.—*The Main Results of Anticoagulant and Antisclerosis Therapy (AC-Tr, Comb-Tr) Compared with Those in the Control Group*

Result of Therapy	All Occasions				Central Vein Occlusions				Main Branch Occlusions			
	AC-Tr, Comb-Tr (37 Cases)		Controls (36 Cases)		AC-Tr, Comb-Tr (26 Cases)		Controls (17 Cases)		AC-Tr, Comb-Tr (11 Cases)		Controls (19 Cases)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Good	22	59	5	14	12	46	--		10	91	5	26
Fair	7	20	10	28	6	23	2	12	1	9	8	42
Poor	5	13	6	16	5	19	2	12	--		4	21
Nil	3	18	15	42	3	12	13	76	--		2	11

22. In 4 the occlusion relapsed after the termination of therapy; 11 had main branch occlusion.

There were 14 men and 19 women, their ages ranging from 41 to 78 years; 7 patients were under 50. Loss of vision in the patients with central vein thromboses was sudden in 13 cases, slow in 7. In main branch thromboses vision had deteriorated rapidly in five patients and gradually in four. No definite information was obtained from four patients. The time from onset to therapy varied from one-half day to two months.

A. Central Vein Occlusions: In this group, the status of the eye when the patient reported for therapy was as follows: Vision was $0.4\frac{1}{\infty}$. Tension was increased in 5 patients; 24 had typical complete occlusion; 2 had incomplete thrombosis. One of the latter (Case 6, Appendix I) also had simple glaucoma in the affected eye and absolute glaucoma in the other eye. The other case (Case 7), again, had the sequela of an old thrombosis in the other eye. The condition of these two seriously sclerotic patients was thus very critical, regardless of the fact that the prognosis is known to be more favorable for incomplete occlusion than for complete occlusion.

As far as patients with central vein occlusion are concerned, the result was good in 46%, fair in 23%, poor in 19%, and nil in 12% (Table 2). The follow-up results are set out in detail in Table 3.

Vision. In 18 cases of central vein occlusion the final vision was better than initial vision. In seven patients it remained nearly unchanged, and in one patient only did the vision deteriorate. Good initial vision, suggesting slight macular damage, seemed promising prognostically, although it was not of decisive significance (Appendix I, Cases 5, 6, 11, and 15). The return to normal vision took only four to eight days in two cases (Cases 7 and 8), but it usually required months. Patients 7 and 8, however, had a relapse. This suggests that therapy was terminated prematurely in these cases.

Visual field. Thinning of the central scotoma was concurrent with the improvement of vision. Metamorphopsia, viz., the distortion of letters, was the last to diminish. It disappeared completely in three cases (Cases 1, 5, and 6).

Tension. Hypertension was established in a total of eight patients. Of these patients,

TABLE 3.—*The Detailed Results Attained With and Without Anticoagulant and Antisclerosis Therapy (AC-Tr, Comb-Tr)*

	With AC-Tr, Comb-Tr	Without AC-Tr, Comb-Tr (Control Group)
Cases, no.	37	36
Vision		
Good result	22	5
Fair result	7	10
Poor or nil result	8	17
Uncertain	--	4
Visual field		
No or mild metamorphopsia	16	6
Severe metamorphopsia or relative central scotoma	10	10
Central and/or peripheral defects	10	16
No information	1	4
Tension		
Normal or controlled	34	28
Uncontrolled sec. glaucoma	2	5
(Enucleation)	(1)	(3)
No information	1	4
Fundus		
No or some hemorrhages and exudates	27	13
Plenty of hemorrhages and exudates	8	15
Collaterals	11	16
Retinal angiosclerosis		
Grade I-II	13	10
Grade III-IV	19	18
No information	2	8
Other eye		
Vision		
Improved	4	2
Worse	1	9
Thrombotic complications	--	2

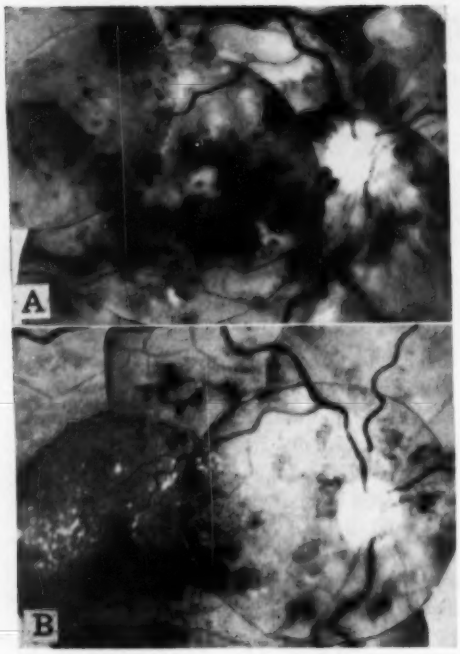

Fig. 1 (Case 15).—A 65-year-old man with a four-week-old occlusion in the right eye. *A*, R. V., H. M. Ocular pressure 35 mm. (Schiøtz). Comb-Tr. *B*, three months later. R. V., 0.15. Glaucoma controlled. Exudates and hemorrhages considerably absorbed. "Hard" exudates remain. Therapy is continued.

five had simple glaucoma. In four cases the tension in the affected eye had risen to 40 to 62 mm. Hg before initiation of the therapy. Despite the glaucoma, a good or fair result was achieved in five cases. Uncontrolled glaucoma developed in only two patients, necessitating enucleation for one of them.

The failures, nil result, were difficult cases, but the therapy was obviously too short in these cases, poorly controlled (Cases 21 and 22), or entirely neglected (Case 7, relapse).

In contrast to the findings of some earlier investigators (Duff et al.[4]), the present results indicate that not even the cases with hypertension on admission for therapy need be automatically considered hopeless.

Changes in the fundus. The resorption of the hemorrhages and edema and even "hard" exudates was generally more rapid than in the control group (Figs. 1 and 2). This was especially so in the cases doing well. The two cases (Appendix I, Cases 7 and 8) in which resorption was extremely rapid prompt the thoughts of the possible thrombolytic effect of heparin.[16,29] The formation of visible collaterals seemed unrelated to the results.

The macular scarring could at a later stage (in spite of continuing therapy for eight months) lead to impairment of vision, although resorption had been fairly rapid (Appendix I, Case 14, Fig. 3).

Recurrent occlusion. Occlusion recurred in four cases after the termination of therapy, although primarily a good result had been achieved. In two of these cases, however, a good end-result was gradually achieved through long-term antisclerosis therapy. In the other two cases therapy could not be resumed.

B. Main Branch Occlusions (Appendix I): The interval from onset to therapy was

Fig. 2 (Case 8).—A 40-year-old man with recurrent occlusion. *A*, state four months after the second attack. R. V., 0.1. Notice "hard" exudates. Comb-Tr. *B*, eight months later. R. V., 0.6. Disturbing metamorphopsia. Slow absorption, but even "hard" exudates are diminished.

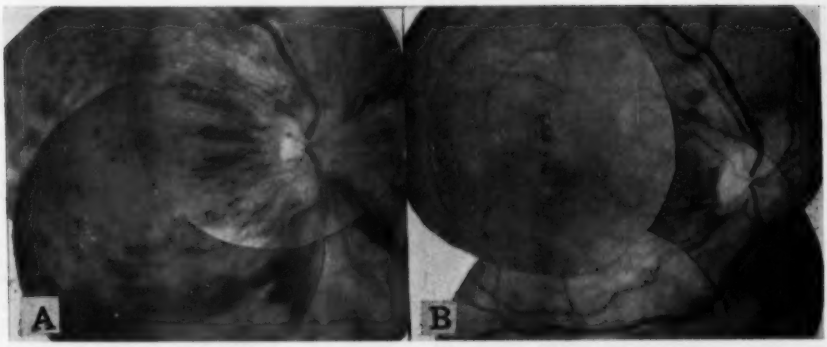

Fig. 3 (Case 14).—A 41-year-old woman with six-week-old occlusion and simple glaucoma. *A*, R. V., 0.15. Ocular pressure, 32 mm. (Schiotz). Comb-Tr continued eight months. Two weeks later, R. V., 0.5. *B*, six months later hemorrhages were absorbed, with macular scarring. Eight months later R. V. was 0.15.

two days to six weeks. Vision in the thrombosed eye varied from 0.6 to finger counting at 2 meters on admission; tension was normal except for a rise to 70 mm. Hg in one patient (Appendix I, Case 29).

Sclerotic manifestations, both in the fundus and elsewhere, spoke for a marked sclerotic component in the pathogenesis of the occlusion. For this, long-term Comb-Tr was given in eight cases and still continues for many of them.

In main branch occlusions, 11 in all, the result was good in 10 cases (91%) and fair in 1 case (9%) (Table 2).

Vision. Vision improved in all 11 cases. The improvement was often gradual, over one-half to one year. Indeed, in one case (Appendix I, Case 25) with poor initial success normal vision was regained first after one and one-half years.

Tension. Hypertension was normalized and kept normal with drops (Cases 24 and 29).

Metamorphopsia. Metamorphosia and/or scotomas also continued to decrease during therapy. But a completely normal field of vision has so far been restored in two cases only.

Fundus. Resorption was fairly rapid also in this group, and the remaining changes were, with the exception of sclerosis of the retinal veins, only slight after one to two years, unlike the position of the control group.

Vision of the "other eye" (Table 3). The vision of the "other eye" improved slightly in several patients during therapy. But mention may be made especially of the cases (Appendix I, Cases 6 and 15) which had had thrombosis of the other eye five and eight years previously, respectively. In these cases vision improved considerably. In nine cases of the control group, again, the vision continued to deteriorate.

Sudden onset and short interval before therapy seemed to be good prognostic factors. On the other hand, a slow onset and long interval before therapy seemed to necessitate particularly long-term therapy.

Therapeutic Complications: Hematuria or subcutaneous hemorrhages occurred during bishydroxycoumarin and phenindione therapy in five patients (21%). In addition, also in five patients, the prothrombin level tended during therapy to "escape" above 40%. None of the hemorrhages proved fatal. After the bleeding, however, many patients were unwilling to continue with the treatment, leading generally to a poor result in consequence of insufficient therapy (Appendix I, Cases 5, 7, 19, and 32).

During intensive heparin medication epistaxis and subcutaneous hemorrhages occurred in one patient (Appendix I, Case 6).

The material of Duff et al. revealed a notable hemorrhagic complication during bishydroxycoumarin therapy in 28% of the cases, and that of Klien and Olwin, in 17%. According to the former authors, a considerable risk attaches to prolonged bishydroxycoumarin therapy. Klien and Olwin, on the other hand, considered the danger of hemorrhage a relatively small risk, deserving attention primarily if the prothrombin "escapes" beyond 30% (with their method). In the present material, 21% of the cases had hemorrhagic complications when drugs of the bishydroxycoumarin type were used. Our related antisclerosis long-term therapy, again, seemed harmless and did not require laboratory control.

II. Patients Not Treated with Anticoagulants Control Group (Appendix II).

Of the 36 occlusions in the 35 patients of the control group, 17 were central vein and 19 were main branch occlusions.

Two cases (Appendix II, Cases 34 and 41) later developed an occlusion also in the fellow eye. Four (Cases 42, 48, 68, and 69) died of cerebral hemorrhage following upon cerebral thrombosis, and one (Case 38) died of coronary thrombosis. These fatalities occurred two and one-half months to one year after the central vein thrombosis.

Fourteen were men and twenty-two were women, ranging in age from 42 to 80 years. Eight were under 50 years of age. The loss of vision in the central vein thromboses was sudden in 11 cases; it was gradual in 4. There is no definite information concerning two of the cases. In the main branch occlusions the loss of vision was sudden in eight cases and gradual in seven; there was no definite information on four cases.

The time between onset and therapy varied from three days to over a year.

A. Central Vein Occlusions: The status of the eyes when the patients reported for therapy was as follows:

Vision was 0.5 to 0. Two patients showed hypertension. The defects of the visual fields were typical, and the fundal changes indicated complete occlusion.

The result was poor or nil in 88% and fair in only 12% of the cases of this group (Table 2). Table 3 gives detailed information on the follow-up results.

Vision. The improvement was modest (final vision 0.2 and 0.15) even in the two cases (Appendix II, Cases 36 and 37) in which a fair result was achieved. Vision improved somewhat during the observation period in only these two cases; in the other patients the vision either remained unchanged or deteriorated.

Tension. Secondary glaucoma developed in five cases (30%), leading in three (Appendix II, Cases 44, 45, and 46) to enucleation.

Visual fields. The visual fields were characterized with one to five years by extensive central scotomas and peripheral scotomas which corresponded to the status of the fundi.

Fundus. These patients generally showed the typical fundus of an old thrombosis. There were, moreover, usually vitreous hemorrhages or massive hemorrhages on the retina, and there were exudates as late as two to three years after the thrombosis, indicative of poor resorption.

Four cases (Appendix II, Cases 34-37) only showed some kind of "spontaneous recovery" (moderate resorption of the hemorrhages). These patients were relatively young (56, 50, 49, and 44 years) and relatively healthy. As regards type, these occlusions were principally stagnation thromboses. However, cicatrization and other changes led in these cases, too, to a fair or poor result, and Case 34 later developed gradually a thrombosis also in the other eye.

Hence, it does seem that the prognosis of complete thromboses, even though the patients received medical treatment but no anticoagulants, is rather hopeless.

There are relatively few earlier reports on the "natural" course of a total occlusion

of the central vein. Moore,[20] Duke-Elder,[5] McLean,[19] and Duff, Falls, and Linman[4] arrived at approximately the same conclusion as above. The extensive statistical material of the last-mentioned investigators comprised 79 followed-up patients; vision had improved in 15% (in our cases, in 12%); in the remainder it was either unchanged or worse; secondary glaucoma developed in 43% (in our cases, in 30%).

A more favorable impression of "spontaneous recovery," however, was obtained by Odqvist[21] and Braendstrup.[2] The latter had 131 cases of occlusions, 15 of them incomplete or main branch thromboses. Sixty-two (47%) developed secondary glaucoma; of the remaining cases, fifty reported for a follow-up. The result was good with 11 of them, fair with 3, and poor or nil with the others. The most manifest difference from the other investigations listed is the good result in 11 cases. The patients of this interesting group were relatively young (average age below 45) and, with the exception of one, they were "healthy" or had only slight hypertension or cardiovascular affection. It is probably in thinking of this group that Braendstrup concludes: "Central vein thrombosis may be said to be an affection with pronounced tendency to spontaneous reparation."

In our control material "young and healthy" cases numbered three only; the tendency to spontaneous recovery, however, was poor, and the final outcome also was poor. In our opinion, central vein occlusions making good progress without special treatment must be considered rare. The tendency to spontaneous healing was in general poorer the more severe the patient's blood pressure and sclerosis. This applies to both complete and main branch thromboses.

B. Main Branch Occlusions (Appendix II): The results in this group were considerably better than in the former: good in 26%, fair in 42%, poor or nil in 32% (Table 2).

In 10 patients vision improved; in the others it remained unchanged or deteriorated.

Secondary glaucoma did occur in a single patient. On the other hand, paracentral, central, and peripheral visual field defects and/or disturbing metamorphopsia occurred even in patients who regained normal vision.

The fundus, even in the cases that made good progress, showed typical changes. The resorption of the hemorrhages and exudates seemed satisfactory only in the cases in which a good result was achieved; others, even two to five years later, showed old hemorrhages and exudates on the retina.

The prognosis seemed to be dependent not only on the seriousness of the original damage to the macula but also on the degree of severity of the general disease leading to the thrombosis.

It may be mentioned by way of comparison that Duff and et al.,[4] from a group of 71 patients, reached practically the same conclusions as we have. In Jensen's[12] group of 42 cases of main branch occlusion, again, initial and final vision did not exceed 0.1 in half of the patients.

Comment

A comparison between the two groups of patients, those receiving AC-Tr and Comb-Tr and those who acted as controls (Tables 2 and 3), shows that the results with the former were superior as regards vision, visual field, fundus changes, and secondary glaucoma. This, notwithstanding the fact that the control group included considerably more main branch thromboses, the prognosis of which is known to be better than that of central vein occlusions. With the therapy administered the recovery of main branch occlusions was good, that of central vein thromboses, variable.

The following factors, especially, seemed to impair the healing of the occlusion: (1) severe systemic diseases, above all arteriosclerosis and high arterial hypertension; (2) late arrival for therapy; this was often the case in the compression occlusions of slow onset; (3) poor initial vision, which points

TABLE 4.—*Results Attained with Anticoagulants in Retinal Venous Occlusion*

	Per Cent			
	Good	Fair	Poor	Nil
Duff, Falls, & Linman [4]				
33 occlusions	33.3	42.5	24.2	
20 complete				
6 incomplete				
7 main branch				
Klien & Olwin [16]				
57 occlusions (3 not accounted for	32.7	21.8	20	25.5
26 complete				
8 incomplete				
14 main branch				
6 smaller branch				
Vannas & Orma				
37 occlusions	50	29	13	8
24 complete				
2 incomplete				
11 main branch				

to serious primary damage of the macula; (4) ocular hypertension.

However, even when the conditions were not propitious, on the four points mentioned above therapy was not always hopeless, provided that it was sufficiently prolonged. Our commonest mistake was ending the therapy too soon. If it was resumed, the conditions were more unfavorable than before.

Table 4 presents the most recent results accomplished with anticoagulant therapy. A common characteristic of all the cases introduced in Table 4 is the use of heparin medication at least at the beginning; also, the therapy was continued in a part of the cases for longer periods. Thus the groups are mutually comparable. Duff, Falls, and Linman [4] and Klien and Olwin [16] used bishydroxcoumarin or other agents lowering the prothrombin level for long-term therapy, while we employed mostly heparin and so-called antisclerosis therapy.

The reports of Hummelt [11] and Scorciarini-Coppola [26] must also be included among the most recent. They, however, employed exclusively synthetic drugs of the bishydroxycoumarin group and on a short-term basis only. In the view of the results of the latter investigator, therapy of this type also improves the prognosis essentially. Hummelt's results, on the other hand, did not differ convincingly from those obtained without anticoagulant therapy.

The results given in Table 4 were considerably better for all the three groups than those of our control material. They were likewise better than the results achieved by the investigators mentioned earlier without anticoagulant therapy. The good result (vision of 1.0 to 0.6) was about the same 33%, in the materials of Duff et al.[4] and Klien et al.[16]; in the present material the result was good in about 59%. As regards fair results, Duff et al. had a proportionately much higher record.

Duff considers short-term intensive heparin therapy to be as good as long-term bishydroxycoumarin treatment. According to Klien, short-term therapy is suitable only in occlusions resulting from stagnation, prolonged therapy, compression, and primary thrombus formations.

Our material indicates that in an obvious case of occlusion by stagnation short-term anticoagulant therapy may prove effective. If sclerosis seemed to be the chief etiological factor of the occlusion, however, short-term therapy did not seem sufficient, even in main branch thromboses. In these circumstances long-term antisclerosis therapy is obviously desirable not only from the standpoint of the patient's eye but also for his life (Cases 9, 38, 42, 48, 68, and 69).

The combined anticoagulant-antisclerosis therapy employed by us in the last five years seems to be rather effective in central vein thromboses. It does seem that other anticoagulants are not able, at least for the time being, to compete successfully with heparin in other respects than ease of dosage and price. The combination of vitamin E with the therapy seemed well-founded and proved beneficial in our experience. In agreement with our results are also the results of biochemical investigations of the last few years into the potential effect of heparin deficiency on the pathogenesis of arteriosclerosis.

It is also interesting to mention the good results of Engelberg et al.[6] in coronary sclerosis with long-term heparinization.

Summary and Conclusions

The investigated material dates from the years 1951-1956 and consists of 75 patients with retinal venous occlusions: a total of 81 thromboses in 77 eyes. Only eight of these patients failed to report for a follow-up. As far as possible, the probable etiology of the occlusion was traced. General sclerotic manifestations either with or without arterial hypertension were diagnosed in 63% of the cases; sclerosis of the fundal veins of the fellow eye was diagnosed in 72%. Mild, moderate, or severe arterial hypertension was established in 71%. An inflammatory factor (usually sinusitis) was found in 13%, and simple glaucoma, in 10%. Sclerosis thus seemed to have an important role in the pathogenesis of the occlusion.

The following therapy was evolved: at first, intensive anticoagulant therapy of 10 days to 3 weeks, preferably with heparin (in exceptional cases with bishydroxycoumarin [Dicumarol] or a corresponding drug). In addition, vasodilator drugs may be employed. Inflammatory etiological factors must also be treated. Then follows in sclerotic cases antisclerosis therapy—100 mg. of heparin sodium intravenously (or 200 mg. subcutaneously) twice a week and 100 mg. of vitamin E per os three times a day. Depending on the patient's condition, the therapy is continued for months or years.

The anticoagulant group consisted of 37 cases of retinal venous occlusion, and the control group, of 36 cases.

The results achieved were as follows (control group in parentheses): good in 59% (14%), fair in 20% (28%), poor in 13% (16%), and nil in 8% (42%). Uncontrolled glaucoma developed in two (five) cases.

Complications: Not very dangerous hemorrhages occurred during bishydroxycoumarin therapy in five cases, and during heparin therapy in one case. Two weeks to six months after termination of short-time anticoagulant therapy recurrent occlusion reappeared in four cases, and one of these also had cerebral thrombosis, but this was not fatal. In the control group there appeared occlusion of the fellow eye in two cases and death with cerebral or coronary thrombosis in five cases. These complications indicate that the state of these patients is perhaps more dangerous without anticoagulant therapy.

Our results indicate that anticoagulant therapy improves considerably the prognosis of central vein occlusion. Even short-term therapy may suffice in some cases. Our experience, however, speaks for the greater efficiency of long-term therapy, especially in elderly patients with a sclerotic etiology.

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(References continued on page 828)

Appendix I. Patients Treated with Anticoagulants (AC-Tr and Comb-Tr)

Case	Age & Sex	Blood Pressure, Systemic Disease	Affected Eye	Onset	Duration Before Therapy	Therapy	Complications of Therapy	Other Eye	Results
Occlusions of central retinal vein: good results									
1	56 F	145/100 Evident stress state (finishing emigration to U.S.A.)	Compl. L.C.V.; L.V.0.3; hemorrhages all over the fundus	Sudden	5 days	Heparin, bishydroxycoumarin 3 wk.		R.V.1.3; fundus n.*; after 5 yr. "normal vision"	After 3 wk. L.V.0.8, hemorrhages considerably absorbed after 5 yr. "normal vision and no distortion of letters" (follow-up letter from U.S.A.)
2	46 M	125/75	Compl. R.L.V.; R.V.0.3; even vitreous hemorrhages	Sudden	11 days	Heparin 8 days, vitamin E 2 mo.		L.V.1.6; ret. angiosclerosis Grade I; after 5 yr. equal	After 1 mo. R.V.1.0; after 5 yr. R.V.0.8, slight metamorphopsia, venous sheathing, collaterals on disc
3	45 M	135/75	Compl. L.C.V.; L.V.0.3; profuse hemorrhages	Slow	2 wk.	Heparin 10 days, vitamin E 2 mo.		R.V.1.0; ret. angiosclerosis Grade I; after 5 yr. R.V. 1.0; ret. angiosclerosis Grade II	After 2 wk. L.V.0.6; edema diminished, remnants of hemorrhages; after 5 yr. L.V.0.6, slight metamorphopsia, ret. angiosclerosis Grade III; macular pigmentation
4	75 M	190/110 Coronary disease, cardiac failure	Compl. L.C.V.; L.V.F.C. at 2 m.; engorged veins, hemorrhages around disc	Slow	5 days	Heparin, bishydroxycoumarin 2 wk.		R.V.1.3; ret. angiosclerosis Grade I; after 4 yr. unchanged	After 2 wk. L.V.0.3; edema disappeared hemorrhages diminished, exudates in macular area; after 4 yr. L.V.0.8; ret. angiosclerosis Grade III; no visible collaterals
5	64 F	120/80 Arteriosclerosis, thromboangiitis obliterans?, simple glaucoma B.E.	Incompl. R.C.V.; R.V.0.1 down to H.M.; hemorrhages near veins and in macula; tension increased	Slow	2 wk.	Heparin, bishydroxycoumarin 19 days; acetazolamide 1 mo.; pilocarpine, heparin, vitamins E & A 9 mo. ——→†	Hematuria after 19 days, heparin reinstated	L.V. no L.P.; complicated cataract; tension controlled after cyclodialysis	After 1 mo. R.V.1.0; tension controlled; hemorrhages diminished, veins engorged and tortuous; after 6 mo. R.V.1.0, no metamorphopsia, hemorrhages and exudates absorbed; some collaterals on disc
6	61 M	180/100, 215/130 Arteriosclerosis, cor pulmonale, pulmonary emphysema, maxillary sinusitis	Incompl. L.C.V.; L.V.0.4.; hemorrhages in macular region, veins engorged and tortuous	Slow	1 mo.	Heparin 3 wk.; penicillin, streptomycin, chlortetracycline, max. puncture, vitamins E & A, heparin 4 mo. ——→	Epistaxis & subcutaneous hemorrhages after 3 wk. (prothrombin 24%, vitamin K & blood transfusion helped)	R.V.0.2; old C.V. occlusion (HCase34); macular scarring; ret. angiosclerosis Grade III; after 2 mo. R.V.0.6, metamorphopsia diminished	After 1 mo. L.V.0.8, slight metamorphopsia; after 4 mo. L.V.1.0, no metamorphopsia, hemorrhages considerably diminished; ret. angiosclerosis Grade III
Recurrent occlusions of central retinal vein: good results in treated attacks									
7	43 M	190/120	Attack I: compl. L.C.V., L.V.0.3; profuse hemorrh.	Sudden	1 day	Heparin, phenindione 4 days	Hematuria after 4 days; therapy discontinued;	R.V.1.6; ret. angiosclerosis Grade II	Rapid recovery, L.V.1.6 in 4 days, venous sheathing
		190/140	Attack II: 2 wk later L.V. F.C. at 1 m.	Sudden	days	3-pyridinemethanol & rutin, pilocarpine	anticoagulant therapy would not be started again		No improvement; after 1 yr. L.V. nil; uncontrolled sec. glaucoma, vitreous hemorrhages, retinal detachment

8	40 M	140/80 Sedim. rate 16	Compl. R.C.V. Attack I: R.V.0.3; hemorrhages all over the fundus	Sudden	1 day	Heparin, phenindione 2 wk., penicillin	L.V.1.3, fundus n.	After 8 days R.V.1.0; hemorrhages and edema rapidly diminished, venous sheathing
		120/70	Attack II: 6 wk. later R.V.0.15, veins engorged, profuse hemorrhages	Slow within 2 days	2 days	Heparin, phenindione 10 days; discontinued for 4 mo., then reinstated heparin & vitamin E & A 4 mo. ⟶	L.V.1.3	After 1 mo. R.V.0.3, hemorrhages slowly diminished; after 4 mo. R.V.0.1, plenty of small hemorrhages all over the fundus, collaterals on disc, "soft and hard" exudates; after 8 mo. R.V.0.6, moderate metamorphopsia, slow absorption of hemorrhages and even "hard" exudates
9	63 M	190/110 Aortic dilatation and sclerosis Cerebral vascular accident 5 mo. later, when considering beginning of Comb-Tr	Attack I: compl. R.C.V., R.V.0.15	Sudden	1 wk.	Heparin, phenindione 2 wk.	L.V.1.0; ret angiosclerosis Grade III	After 1 mo. R.V.0.6, edema and hemorrhages diminished
			Attack II: 5 mo. later R.V. 0.3., veins engorged, profuse new hemorrhages	Slow		Vasolastine (new antisclerosis remedy) 4 mo., vitamins E & A 2 mo. ⟶	L.V.1.0; veins engorged	After 2½ mo. L.V.0.6; metamorphopsia, ret. angiosclerosis Grade IV, extensive attenuation of retinal arterioles; some collaterals on disc and punctuate hemorrhages around macula
10	55 M	180/100 Allergic constitution; septic teeth	Attack I: compl. R.C.V., R.V.0.3, profuse hemorrhages all over the fundus	Slow	4 days	Heparin, bishydroxycoumarin 2 wk., vitamin E, penicillin, dental cure	L.V.1.6; fundus n.	After 2 wk. R.V.0.6., edema disappeared, hemorrhages partly absorbed
			Attack II: 3 mo. later examined elsewhere	Slow	No treatment			After 5 yr. R.V.0.15; metamorphopsia, relative paracentral scotoma; collaterals on disc, venous sheathing, vitreous hemorrhages, macular scarring
Occlusions of central retinal vein: fair results								
11	55 M		Compl. R.C.V.; R.V.F.C. at 0.5 m. hemorrhages especially in macular area	Sudden	10 hr.	Heparin, bishydroxycoumarin 12 days	L.V.1.3; ret. angiosclerosis Grade II; after 5 yr. unchanged	After 12 days R.V.F.C. at 0.5 m., hemorrhages partly absorbed; after 5 yr. R.V.0.3; small paracentral scotoma, ret. angiosclerosis Grade III, macular degeneration, no hemorrhages
12	46 M	150/90 Coronary disease, maxillary sinusitis, after 2½ yr. anginal attack	Compl. R.C.V.; R.V.0.3	Slow	3 wk.	Heparin 4 days, penicillin, max. puncture; after 2½ yr. heparin 7 days	L.V.1.0; ret angiosclerosis Grade II; after 3 yr. L.V.1.3	After 6 wk. R.V.0.4, acute attack of sec' glaucoma, controlled; after 3 yr. R.V.0.5, tension normal, slight metamorphopsia; veins dilated tortuous; small hemorrhages
13	64 F	210/110 Coronary disease, cardiac failure, simple glaucoma L.E. and absol. R.E.	Compl. L.C.V.; L.V.F.C. at 1 m. O.P. 40 mm. (Schiötz); profuse hemorrhages, glaucomatous excavation	Slow	2 mo.	Heparin, bishydroxycoumarin 14 days, pilocarpine; after 1½ yr. vitamins E & A, heparin 2 mo. ⟶	R.V. nil; glaucomatous excavation, ret. angiosclerosis	After 2 wk. L.V.F.C. at 3 m., tension controlled; after 1½ yr. L.V.0.15, tension controlled; after 1 yr. 8 mo. L.V.0.25, glaucomatous excavation, ret. angiosclerosis Grade III, no hemorrhages, macular pigmentation
14	41 F	135/95 Influenza, simple glaucoma B.E.	Compl. R.C.V.; R.V.0.15, profuse hemorrhages and exudates, hole in macula?	Sudden	6 wk.	Heparin i. v. and locally 1 mo.; pilocarpine, vitamins E & A, heparin 8 mo.	L.V.1.0; ret. angiosclerosis Grade I; after 8 mo. unchanged	After 2 wk. R.V.0.5; tension controlled, hemorrhages partly absorbed; after 8 mo. R.V.0.15, central scotoma, macular scarring, no hemorrhages

Appendix I. Patients Treated with Anticoagulants (AC-Tr and Comb-Tr)—Continued

Case	Age & Sex	Blood Pressure, Systemic Disease	Affected Eye	Onset	Duration Before Therapy	Therapy	Complications of Therapy	Other Eye	Results
15	65 M	200/110 Coronary disease	Compl. R.C.V.; R.V.H.M.; O.P. 35 mm. (Schiøtz); massive hemorrhages in macular area and all over the fundus	Slow	4 wk.	Heparin i. v. and locally 4 wk.; pilocarpine, vitamins E & A, heparin 4 mo. ——→		L.V.0.3; fundus: old C.V. occl., angiosclerosis Grade III, macular scarring; after 2 mo. L.V.0.5	After 4 mo. R.V.0.2; glaucoma controlled, central relative scotoma; exudates, hemorrhages considerably absorbed; even "hard" exudates (Fig. 1) diminished
Occlusions of central retinal vein: poor or nil results.									
16	61 F	145/95 Coronary disease	Compl. R.C.V.; R.V.F.C. at 1 m.	Sudden?	10 days	Heparin, bishydroxycoumarin 10 days	Prothrombin occasionally over 40%	L.V.1.0; ret. angiosclerosis Grade I	After 10 days R.V.F.C. at 2 m., lens opacities; after 5 yr. R.V.F.C. at 2 m., central scotoma, remnants of hemorrhages
17	54 F	190/110 Cardiac enlargement, maxillary sinusitis	Compl. R.C.V.; L.V. 0.1	Sudden	3 wk.	Heparin, 10 days penicillin		R.V.1.3; fundus n.; after 2½ yr. R.V.1.0; ret angiosclerosis Grade III	After 10 days L.V.0.3, hemorrhages partly absorbed; after 2½ yr. L.V.F.C. at 3 m., severe metamorphopsia; angiosclerosis Grade III, venous sheathing, collaterals on disc, macular degeneration
18	71 F	220/120 Coronary disease	Compl. R.C.V.; R.V.L.P., profuse hemorrhages, even in vitreous	Sudden	1 day	Heparin, bishydroxycoumarin 7 days		L.V.0.6; ret. angiosclerosis Grade III; after 2½ yr. equal	After 1 wk. R.V.F.C. at 2 m.; after 2½ yr. R.V.F.C. at 3 m., central scotoma, ret. angiosclerosis Grade III, pale disc, macular degeneration
19	78 F	160/85 Arteriosclerosis, Hypochromic anemia	Compl. L.C.V.; L.V.F.C. at 0.5 m.; even vitreous hemorrhages	Sudden	4 days	Heparin, phenindione 5 days, vitamin E	Subcutaneous hemorrhages, AC-Tr discontinued	R.V.1.0; ret. angiosclerosis Grade III; after 1 yr. equal	After 2 wk. L.V.F.C. at 4 m.; after 1 yr. L.V.F.C. at 3 m., central scotoma, collaterals on disc, ret. angiosclerosis Grad e III, remnants of hemorrhages and exudates macular scarring
20	73 F	170/90 Arteriosclerosis	Compl. R.C.V.; R.V.F.C. at 2 m., massive hemorrhages and edema	Sudden	3 wk.	Heparin, phenindione 12 days	Prothrombin occasionally over 40%	L.V.1.0; ret. angiosclerosis Grade II; after 1 yr. unchanged	After 12 days R.V.F.C. at 4 m.; after 1 yr. R.V.F.C. at 3 m., paracentral scotoma, numerous collaterals, macular scar, no hemorrhages
21	78 M	205/90 Arteriosclerosis, simple glaucoma B.E.	Compl. R.C.V.; R.V.H.M.; O.P. 67 mm.; (Schiøtz) profuse hemorrhages and exudates	Slow	4 wk.	Phenindione 11 days, pilocarpine	Prothrombin occasionally over 40%	L.V.0.6; ret. angiosclerosis; no glaucomatous excavation; after 1½ yr. L.V.0.8.	After 11 days R.V.H.M., glaucoma controlled; after 1½ yr. R.V.H.M., O.P. 28 mm. (Schiøtz); pale disc, glaucomatous excavation, no hemorrhages
22	70 F	200/100 Arteriosclerosis, simple glaucoma B.E.	Compl. L.C.V.; L.V.H.M.; O.P. 40 mm.; (Schiøtz) profuse hemorrhages, even in vitreous	Sudden	1 wk.	Heparin, phenindione 2 wk., pilocarpine; after 10 mo. acetazolamide		R.V.1.0; ret. angiosclerosis Grade II; after 1 yr. R.V.1.0; O.P. 35 mm. (Schiøtz); small ret. hemorrhages	After 2 wk. L.V.F.C. at 0.3 m. glaucoma controlled, hemorrhages in abundance; after 10 mo. L.V. nil, enucleation for uncontrolled glaucoma; dissection: pale disc, no ret. hemorrhages
Main branch occlusions: good results									
23	46 M	105/60	L. sup. branch; L.V.0.6	Sudden	1 wk.	Heparin, bishydroxycoumarin 2 wk.		R.V.1.3; fundus n.	After 4½ yr. L.V.1.0; no metamorphopsia; nasal sup. disc margin hazy

24	57 F	190/90 Polycythemia vera; simple glaucoma B.E.	R. sup. branch; R.V.0.4; profuse hemorrhages, ret. angiosclerosis Grade II	Sudden?	4 wk.	Heparin, bishydroxycoumarin 2 wk.; vitamin E 2 mo., pilocarpine		L.V.0.4; glaucomatous excavation; after 2 yr. L.V.0.3.	After 2 wk. R.V.0.5; after 2 yr. R.V.0.8; mild metamorphopsia, tension controlled, hemorrhages absorbed
25	62 F	190/110 Coronary disease	R. sup. branch; R.V.0.1; ret. angiosclerosis Grade III; massive hemorrhages in macular area	Sudden	2 days	Heparin, bishydroxycoumarin 3 wk.; vitamins E & A and heparin by turns 2 yr.		L.V.1.0; ret. angiosclerosis Grade II; after 2 yr. L.V. 1.3; fundus equal	After 4 wk. R.V.0.3; after 6 mo. R.V.0.6; after 1½ yr. R.V.1.0, slight metamorphopsia; after 2 yr. R.V.0.8; ret. angiosclerosis Grade III, some collaterals, hemorrhages absorbed; slight pigment deposits in macula
26	60 F	160/90 Arteriosclerosis	L. sup. branch; L.V.0.3; macular hemorrhages, ret. angiosclerosis Grade III	Slow	4 wk.	Heparin, phenindione 2 wk.; vitamin E		R.V.0.8; ret. angiosclerosis Grade III; after 1 yr. R.V.1.0	After 2 wk. L.V.0.6, hemorrhages partly absorbed; after 2 yr. L.V.1.0, no metamorphopsia, ret. angiosclerosis Grade III, small hemorrhages
27	61 F	170/100 Cardiac failure, cerebral sclerosis	L. inf. branch; L.V.0.6; hemorrhages, visible collaterals	Slow	6 wk.	Heparin, bishydroxycoumarin 2 wk.		R.V.1.0, ret. angiosclerosis Grade II; after 2 yr. unchanged	After 2 wk. L.V.0.6; after 2 yr. L.V.0.8, slight metamorphopsia, ret. angiosclerosis Grade II, no hemorrhages, slight macular degeneration
28	70 F	220/115	R. sup. branch; L.V.0.25; ret. angiosclerosis	Sudden	12 days	Heparin, phenindione 3 wk.	Prothrombin occasionally over 40%	L.V.1.0; ret. angiosclerosis; after 1½ yr. L.V.1.3	After 3 wk. R.V.1.0; after 1½ yr. R.V.0.8, metamorphopsia, ret. angiosclerosis Grade II, no hemorrhages, slight macular degeneration
29	67 M	120/60 Arteriosclerosis	L. inf. branch; L.V.F.C. at 2 m.; O.P. 70 mm. Schiötz; profuse hemorrhages, even in macula	Sudden	2 wk.	Heparin 2 wk.; acetazolamide, pilocarpine, heparin locally, vitamins E & A 10 mo. ⟶		R.V.0.8, ret. angiosclerosis Grade II; after 6 mo. R.V.1.0	After 6 wk. L.V.0.3, glaucoma controlled; after 8 mo. L.V.0.6., moderate metamorphopsia, ret. angiosclerosis Grade II, some collaterals on disc, no hemorrhages, slight macular scarring
30	54 F	220/130 Pernicious anemia; coronary disease	R. sup. branch; R.V.0.5; ret. angiosclerosis Grade III	Sudden	1 wk.	Heparin, phenindione 9 days; after 6 mo. vitamins E & A and heparin again ⟶	Subcutaneous hemorrhages; treatment discontinued	L.E. enucleated earlier	After 9 days R.V.1.0; hemorrhages partly absorbed, still exudates; after 6 mo. R.V. 1.3; still hemorrhages; metamorphopsia
31	67 F	230/110 Arteriosclerosis	R. sup. branch; R.V.0.3; massive hemorrhages down into macula, ret. angiosclerosis Grade II	Sudden	2 mo.	Heparin, phenindione 6 wk.; vitamins E & A ⟶		L.V.1.0; ret. angiosclerosis Grade II	After 6 wk. R.V.0.5, paracentral scotoma, hemorrhages partly absorbed; after 3 mo, R.V.0.6, hemorrhages more absorbed, small exudates
32	67 F	160/100 Arteriosclerosis	L. sup. branch; L.V.0.5	Slow	2 wk.	Heparin, phenindione 7 days; after 11 mo. heparin & vitamins E & A 2 mo. ⟶	Subcutaneous hemorrhage ; treatment discontinued	R.V.0.8; ret. angiosclerosis Grade II; after 13 mo. equal	After 2 mo. L.V.0.4; after 11 mo. L.V.0.2, numerous collaterals, still hemorrhages and exudates, metamorphopsia; after 13 mo. L.V.0.6, hemorrhages and exudates diminished
Main branch occlusions: fair results									
33	67 F	200/120 Cerebral sclerosis, diabetes mellitus	L. inf. branch; L.V.0.1; massive hemorrhages, ret. angiosclerosis Grade III	Slow	?	Heparin, bishydroxycoumarin 2 wk.; vitamins E & A & heparin 4 mo. ⟶	Prothrombin occasionally over 40%	R.V.0.8, ret. angiosclerosis Grade II	After 4 mo. L.V.0.4; paracentral scotoma, still hemorrhages and exudates

* n., normal.
†⟶, therapy is still going on.

Appendix II. Patients Not Treated with Anticoagulants (Control Group)

Case	Age	Sex	Blood Pressure, Systemic Disease	Affected Eye	Onset	Duration Before Therapy	Other Eye	Results
Occlusions of central retinal vein: fair results								
34	49	F	180/100 Sedim. rate 21	Compl. R.C.V.; R.V.F.C. at 3 m., hemorrhages all over the fundus	Sudden	1 wk.	L.V. 1.0; ret. angiosclerosis Grade I; after 2 yr. equal	After 2 yr. R.V. 0.2, relative central scotoma and severe metamorphopsia; numerous collaterals on disc, ret. angiosclerosis Grade III, venous sheathing, macular scar
35	44	F	110/85	Compl. L.C.V.; L.V.F.C. at 3 m.	Sudden	3 mo.	R.V. 1.3; ret. angiosclerosis Grade I; after 1 yr. equal	After 1 yr. L.V. 0.15, central scotoma, collaterals on disc, dilated veins, venous sheathing, ret. angiosclerosis Grade III, macular degeneration
Occlusions of central retinal vein: poor or nil results								
36	56	M	225/120	Compl. R.C.V.; R.V.F.C. hemorrhages especially near macula	Sudden	4 wk.	L.V. 1.0, fundus n.; after 5 yr. L.V. 1.0; ret. angiosclerosis Grade IV; after 5 ½ yr. C.V. occl. (I Case 6)	After 5 yr. R.V. F.C. at 3 m., central scotoma, ret. angiosclerosis Grade IV, macular scarring
37	50	M	130/100	Compl. L.C.V.; L.V. F.C. at 1 m; even vitreous hemorrhages	Sudden	2 wk.	R.V. 1.3.; after 3 yr. R.V. 1.3.; ret. angiosclerosis Grade II	After 3 yr. L.V. F.C. at 2 m., central scotoma; profuse vitreous opacities
38	69	F	220/120 Coronary disease; cardiac failure; auricular fibrillation	Compl. L.C.V.; L.V. F.C. at 0.5 m.; even vitreous opacities	Slow	?	R.V.0.6, incipient cataract	After 6 mo. L.V. H.M., hemorrhages remained; after 1 yr. died of arteriosclerotic heart disease
39	74	F	185 Coronary disease	Compl. R.C.V.; R.V. F.C. at 1 m.	Slow	6 mo.	L.V. 0.8; ret. angiosclerosis Grade I-II; after 2 yr. equal	After 4 yr. R.V. F.C. at 1 m., extensive scotoma, no sec. glaucoma, hemorrhages and exudates remain
40	70	M	130/90 Coronary disease, diabetes mellitus, simple glaucoma B.E.	Compl. L.C.V.; L.V. F.C. at 0.5 m.; hemorrhages all over the fundus	Slow	3 wk.	R.V. 1.3; after 4 yr. R.V. 1.0., ret. angiosclerosis Grade II	After 1 yr. L.V. H.M., uncontrolled glaucoma; after 4 yr. L.V. nil, fundus cannot be seen
41	64	F	235/110 Arteriosclerosis	Compl. R.C.V.; R.V. F.C. at 2 m.	Sudden	3 wk.	L.V. 1.0; ret. angiosclerosis Grade III; after 1 yr. occlusion & sup. branch (II Case 55)	After 1 yr. R.V. F.C. at 1.5 m., collaterals on disc, ret. angiosclerosis Grade IV, still hemorrhages; after 3 ½ yr. R.V.L.P., vitreous hemorrhages
42	80	M	Arteriosclerosis coronary disease	Compl. R.C.V.; R.V. F.C. at 1.5 m.; macular degeneration, too	Sudden	3 days	R.V. 0.3, angiosclerosis Grade IV, macular degeneration	After 5 mo. died of cerebral hemorrhage and bronchial pneumonia
43	43	F	230 Polycythemia vera	Compl. L.C.V.; L.V. L.P.; profuse hemorrhages	Sudden	1 wk.	R.V. 1.3.; after 3 yr. R.V. 1.3, angiosclerosis Grade I	After 3 yr. L.V.=no L.P., still profuse hemorrhages and exudates
44	71	M	180/100 Arteriosclerosis, coronary disease, cardiac failure, diabetes mellitus	Compl. L.C.V.; L.V. F.C. at 1.5 m.	Slow	2-3 mo.	R.V. 0.8., ret. angiosclerosis Grade II; after 3 yr. R.V. 0.6, ret. angiosclerosis Grade III	After 3 yr. L.V. F.C. at 0.5 m., central scotoma, pale disc, margin hazy, ret. angiosclerosis Grade III, still hemorrhages and exudates; 1 mo. later enucleation for secondary glaucoma
45	67	M	230/140 Coronary disease	Compl. R.C.V.; R.V. L.P.	Sudden	1 wk.	L.V.0.4, incipient cataract	After 2 ½ yr. R.V. nil, enucleation for secondary glaucoma
46	64	F	195/110 Arteriosclerosis	Compl. R.C.V.; R.V. nil, O.P. 90 mm. (Schiøtz)	Sudden	2 mo.	L.V.0.8; ret. angiosclerosis Grade II	Enucleation for uncontrolled secondary glaucoma; venous occlusion is certified by histologic examination

47	75	F	220 Arteriosclerosis	Compl. L.C.V.; L.V.0.25	Sudden	6 wk.	R.V.1.0. ret angiosclerosis Grade II; after 1 ½ yr. R.V.0.8.	After 1 ½ yr. L.V. H.M., numerous collaterals. ret. angiosclerosis Grade IV, macular degeneration and exudates
48	49	M	200 Cerebral sclerosis	Compl. R.C.V.; R.V.0.5	Slow		L.V.1.0; ret. angiosclerosis Grade III	Died after 3 mo. of cerebral thrombosis
49	73	F	210/105 Coronary disease cardiac failure	Compl. R.C.V.; R.V. F.C. at 0.3 m.	Slow?	5 mo.	L.V.1.0, ret. angiosclerosis Grade III	After 1 yr. R.V. F.C. at 0.5 m., central scotoma, collaterals on disc, still hemorrhages and exudates, ret. angiosclerosis Grade III
50	77	M	Coronary disease cardiac failure	Compl. L.C.V.; L.V. F.C. at 1 m.	Sudden	1 wk.	R.V.1.0, ret. angiosclerosis Grade III	After 4 mo. L.V.=no L.P., still profuse hemorrhages
Main branch occlusions: good results								
51	56	F	150/85 Coronary disease	R. sup. branch; R.V.0.4	Slow	3–4 mo.	L.V.1.0, fundus n.; after 3 ½ yr. L.V.1.0, ret. angiosclerosis Grade I	After 3 ½ yr. R.V.1.0; slight metamorphopsia, collaterals on disc, ret. angiosclerosis Grade II
52	54	F	220/110 Pulmonary tuberculosis	R. sup. branch; R.V.0.8	Slow?	2 mo.	L.V.1.0, fundus n.; after 3 ½ yr. L.V.1.3, ret. angiosclerosis Grade II	After 3 ½ yr. R.V.1.0; severe metamorphopsia, collaterals, venous sheathing, ret. angiosclerosis Grade III, synchysis scintillans
53	42	M	130/80 Angina pectoris	L. sup. branch; L.V.0.5, small hemorrhages in macula	Sudden	4 wk.	R.V.1.0, ret. angiosclerosis Grade I; after 3 yr. R.V.1.3	After 3 yr. L.V.1.0; no metamorphopsia, but peripheral visual field defect; venous sheathing, ret. angiosclerosis Grade I, punctate hemorrhages in macula
54	52	F	155/105	R. inf. branch; R.V.0.4	Sudden	3 days	L.V.1.0, ret. angiosclerosis Grade I; after 2 yr. equal	After 2 yr. R.V.0.8, slight metamorphopsia, collaterals on disc, ret. angiosclerosis Grade I
55	66	F	235/110 Arteriosclerosis	L. sup. branch; L.V.0.4	Sudden	3 days	R.V.F.C. at 2 m., old C.V. occl., after 2 yr. R.V.H.M. vitreous hemorrhage	After 2 yr. L.V.1.0, ret. angiosclerosis Grade IV, numerous collaterals, pigment deposits in macula
Main branch occlusions: fair results								
56	76	M	210/110 Arteriosclerosis	L. sup. branch; L.V.0.3, hemorrhages even in macula	Slow?	3–4 mo.	R.V.1.0; after 4 ½ yr. R.V.0.5, lens opacities	After 4 ½ yr. L.V.0.3, metamorphopsia, ret. angiosclerosis Grade III, macular pigment, hemorrhage in periphery
57	49	F	275/150 Nephrosclerosis	L. inf. branch; L.V.F.C. at 5 m., many hemorrhages	Sudden?	3 wk.	R.V.1.0, ret angiosclerosis Grade II; after 2 yr. equal	After 2 yr. L.V.0.5, metamorphopsia and paracentral scotoma, collaterals and venous sheathing, slight macular degeneration, ret. angiosclerosis Grade III
58	73	F	220/110; after 2 yr. 255/115	L. sup. branch; L.V.0.3, ret. angiosclerosis Grade II	Sudden?	4 wk.	R.V.1.0, ret. angiosclerosis Grade I; after 2 yr. equal	After 2 yr. L.V.0.3, severe metamorphopsia, ret. angiosclerosis Grade III, still hemorrhages small exudates, pigment in macula
59	60	M	155/90 Cerebral hemorrhages 3 yr. earlier	L. sup. branch; L.V.0.4	Slow	10 days	R.V.1.0, ret. angiosclerosis Grade II; after 2 ½ yr. equal	After 2 ½ yr. L.V.0.3, severe metamorphopsia, angiosclerosis Grade IV, collaterals, punctate hemorrhages and small exudates in macula
60	51	F	245/150 Aortic aneurysm, treated neurosyphilis	R. inf. branch; R.V.0.1, hemorrhages into macula, ret. angiosclerosis Grade II	Slow	6 wk.	L.V.1.0, ret. angiosclerosis Grade II; after 3 yr. equal	After 3 yr. R.V.0.5, severe metamorphopsia, ret. angiosclerosis Grade III, collaterals and venous sheathing, pigmented scar and small exudates close to macula
61	75	F	220/80 Arteriosclerosis	R. sup. branch; R.V.0.15, hemorrhages into macula, ret. angiosclerosis Grade II	Slow	4 wk.	L.V.1.0, ret. angiosclerosis Grade I; after 2 yr. L.V.0.6, ret. angiosclerosis Grade II macular degeneration	After 2 yr. R.V.0.25, metamorphopsia, paracentral scotoma, numerous collaterals on disc, still hemorrhages, macular scarring
62	80	F	240; after 6 mo. 195/85	R. sup. branch; R.V.0.6, ret. angiosclerosis Grade III	Sudden	3 wk.	L.V.F.C. at 2 m., ret. angiosclerosis Grade IV; after 6 mo. L.V.F.C. at 1 m.	After 6 mo. R.V.0.5, metamorphopsia, angiosclerosis Grade IV, many hemorrhages still

63	70	M	200/100		L. sup. branch; L.V.F.C. at 2 m., even vitreous hemorrhages	Slow	1 yr.	R.V.0.8, ret. angiosclerosis Grade II; after 3 yr. equal	After 3 yr. L.V.0.1, metamorphopsia and peripheral visual field defect, disc margin hazy, venous sheathing, collaterals, and small hemorrhages, macular scarring and hemorrhages, ret. angiosclerosis Grade II
Main branch occlusions: poor or nil results									
64	56	M	170/110 Arteriosclerosis		R. sup. branch; R.V.0.3, extensive ret. hemorrhages	Sudden	4 wk	L.V.1.0, ret. angiosclerosis Grade II; after 3 yr. equal	After 3 yr. R.V.F.C. at 2 m., central scotoma, numerous collaterals on disc, ret. angiosclerosis Grade III, hemorrhages
65	66	F	250 Diabetes mellitus		L. inf. branch; L.V.0.4, ret. angiosclerosis Grade III	Slow		R.V.1.0, ret. angiosclerosis Grade II; after 2 yr. equal	After 2 yr. L.V.F.C. at 3 m., paracentral scotoma, ret. angiosclerosis Grade III; still hemorrhages and exudates, even in macula
66	74	F	210/120 Coronary disease		L. inf. branch; L.V.F.C. at 1 m., ret. angiosclerosis Grade II	Sudden	2 wk.	R.V.0.8, ret. angiosclerosis Grade I; after 2 yr. R.V.1.0	After 2 yr. L.V.F.C. at 4 m., central scotoma, collaterals in disc, ret. angiosclerosis Grade III, extensive macular scarring
67	48	M	215/130		R. inf. branch; R.V.F.C. at 5 m.	Sudden	2 wk.	L.V.1.6, ret. angiosclerosis Grade II; after 1 yr. L.V. 1.3	After 1 yr. R.V.F.C. at 4 m., large visual field defect into fixation point, ret. angiosclerosis Grade II, venous sheathing, profuse hemorrhages and exudates
68	65	F	170/110 Aortic sclerosis		R. sup. branch; R.V.0.5	Slow	4 wk.	L.V.1.0	Died after 6 mo., of cerebral hemorrhages
69	58	F	250 Coronary disease, cardiac failure		R. inf. branch; R.V.0.3	Sudden	3 wk.	L.V.1.0	After 8 mo. "eye became slowly blind"; died after 9 mo. of cerebral hemorrhage and pneumonia

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Experimental Studies of the Choroidal Vessels

VI. Observations on the Effects of Physical Agents (Scleral Folding and Diathermy)

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In the present study, the actions of physical agents on the choroid will be considered as participating in surgical procedures.*

The basic principle of the cure of retinal detachment involves the closure of the retinal breaks. The rational basis for this therapy was established by Gonin's [2-21] concept of direct correlation between retinal holes and retinal separation.

One of the additional requirements for a successful procedure involves the approximation of the detached retina to the pigment layer and to its matrix, the choroid.[22] This can be accomplished by a reduction in volume of the scleral coat through either thermal shrinkage or mechanical shortening.

A. Heat shrinkage of the sclera. Heat has been noted to reduce the volume of the scleral coat.[23] Berens and Pischell [24] and others observed clinically the shrinking of the sclera induced by electrocoagulation during surgery for retinal detachment. Scheie and Jerome [25] demonstrated experimentally that diathermy produces shrinkage of the sclera at the site of application, with a rapid rise of intraocular pressure, indicating a reduction of volume. They found that 14 applications of surface coagulation caused an 18.5% reduction in volume on enucleated eyes and a 10.6% reduction on eyes of living animals. Scleral resection of 4 by 22 mm. performed in enucleated eyes induced a volumetric decrease of 13.3%. When 30 applications of penetrating diathermy were used in living dogs, a 6% reduction occurred.

B. Mechanical shortening of the sclera. Several procedures have been evolved for mechanical shortening of the globe. They have as a common characteristic a volumetric decrease without a concomitant reduction in the surface available for the settlement of the detached retina. The development of the various techniques will be described in more or less chronological sequence for the purpose of showing their historical relationships.

Mechanical Agents: Sceral Folding

1. *Perforating, or Total, Scleral Resection.*

Such an operation was originally reported by Müller,[26-30] in 1903, for cases of retinal detachment in high degrees of myopia. He believed that an increased distention of the choroid in myopes causes inflammatory changes leading to transudation and retinal detachment. Müller attributed the beneficial effects of his operation not to the diminution of the size of the eyeball but to relief of tension on the choroid, which improves its blood circulation and removes the cause for a transudate to form between choroid and retina. The operation consisted in the resection of an ellipse from the temporal half of the sclera measuring 10 by 20 mm. followed by drainage of the subretinal fluid. In his first cases he employed an approach according to the method of Kronlein.

The original procedure underwent several modifications introduced by Müller,[26-30] Elschnig,[31,32] and Blaskovics.[33] The last-

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* These investigations were carried out in living albino rabbits. The technique for observation of the choroidal circulation through the outer ocular coats has been previously described.[1]

named author advised one to carry the original elliptic incision only half way through the thickness of the sclera and to remove the superficial layers of the flap. The sutures were then inserted and the posterior border of the incision was carried through the entire thickness of the sclera. The choroid was then separated from the sclera, and, by drawing the sutures together, the anterior and posterior wound edges were united and at the same time the flap was pushed into the suprachoroidal pocket.

Among others who adopted the operation were Czermak,[34] Schultz,[35] Holth,[36] Leitner,[37] Torok,[38,39] Schiötz,[40] Lenz,[41] and Koch.[42] The total number of resections reported by these early authors was 82. Cures were claimed in approximately 22% of the cases, and improvement, in 30%. The results were remarkably good when compared with other methods of operation used at that time.[43]

With the recognition of Gonin's [2-21] work in the cure of retinal detachment, scleral resection was shelved until 1933, when it was revived by Linder [44-50] for selected cases. This author introduced the resection of longer (up to full circumference in stages) and narrower strips. It is largely his technique that has been followed since. Other early observations were made by Guist [51] and Hildesheimer,[52] who published their experiences with various methods used to decrease the size of the scleral coat.

The development of new techniques stimulated renewed interest in the operation. Perforating scleral resection was performed by some surgeons who reported remarkable success considering the desperate nature of the cases usually selected. Leopold [53] was able to collect 121 cases from the world literature up to 1945, of which 25 had successful reattachment and 31 had partial or temporary reattachment. Reports concerning the procedure have been made, among others, by Brown and Bothman [54]; Ramach [55]; Pischel, Kronfeld, and Miller [56-59]; Borley [43,60]; Vail [61-63]; Bogart [64]; Sobanski [65]; Ahuja [66]; Philips, Lister, and Shapland [67-72]; Mejer [73,74]; Fanta [75,76]; Hruby [77-83]; Ayoub [84]; Castroviejo and Torres-Lucena [85,86]; Vesey [87]; Thorpe [88]; Robertson [89]; Hughes [90]; Dunnington [91]; Gasteiger [92]; Schreck [93]; Csapody [94]; Gormaz,[95] and Fu-Shing.[96]

Because of its technical difficulties and the severe complications (hemorrhages, loss of vitreous, rapid shrinkage of the globe), total scleral resection never gained wide acceptance and its performance is relatively infrequent.

2. Partial, or Lamellar, Scleral Resection.

Because of the hazards of complete scleral resection, Lindner,[97] in 1949, described an operation in which shortening of the eyeball was accomplished by the folding of a surgically thinned sclera. The clinical indications, the efficacy of this procedure, and some technical variations have been annoted in, by now, an extensive literature, represented in the contributions of Shapland [98-104]; Paufique, Hugonnier, Rougier, Bonamour, and Spira [105-108]; Cross [109]; Philips [110]; Lloyd [111]; Friemann [112]; Berliner [113,114]; Nicolato [115]; Barut [116]; Stallard [117]; Basterra [118]; Gormaz and Verdaguer [119,120]; Valiere-Vialeix and Robin [121]; Infante [122]; Bohringer [123]; Mercier [124]; Koenig [125]; Bouchel [126]; Safar [127]; Salgado-Gomez [128]; Hitz [129]; McDonald [130]; Arruga [131]; Nataf, Besnainou, Reynon, and Spaier [132]; Bengisu [133]; Schiff-Wertheimer, Gaillard, and Figueroa [134]; Macrae and Cowan,[135] and Staz.[136]

Several modifications and combinations of the classical procedure have been advocated. Norton [137] follows the technique based on the work of Schepens and Okamura,[138-140] in which the resection is done directly over the retinal break or slightly posterior to it and the choroid is deeply invaginated by the use of a polyethylene tube buried in the bed of the resection at the time of closure. Chamlin and Rubner [141] utilize Schepens' principle of adding some bulk to the folded sclera. This is accomplished by undermining a scleral lamella that contracts into a narrow, cord-like strip, re-

maining in the center of the groove, where it retains its original attachment to the deeper layers of the sclera. While the scleral edges are being approximated the undermined lamella is buried in the buckle, thus helping to create a more pronounced fold.

Meek [142,143] advocates a shortening of the sclera in the anterior-posterior diameter by a resection parallel to the limbus, and he also removes a piece of sclera perpendicular to the midpoint of the first resection, so as to shorten the eye from side to side. In cases where it is necessary to produce maximum reduction in ocular volume, Barraquer and Muinos [144,145] recommended a criss-crossed resection. The meridional resection is perpendicular to the anterior one and goes from the ora serrata to the most posterior portion which the operating field permits.

Jayle and Ourgaud [146,147] have proposed a lamellar resection with a rectangular flap hinged posteriorly. The resected area is closed by approximating the hinged posterior edge to the free anterior edge with mattress sutures. The scleral flap is then pulled over the previously sutured edges and fixed anteriorly to the sclera with a running suture.

The study of scleral resections from an experimental and a histological approach has been described in the works of Guist [51]; Borley [43,60]; Scheie and Jerome [25]; Fanta [148]; Dellaporta [149-154]; Paufique, Hugonnier, and Moreau [155]; Fry, Kasser, and DeLong [156]; Everett [157,158]; Asbury and Vaughan,[159] and McGavic.[160]

3. *Complete Folding, or Tucking, of the Sclera.*—This shortening procedure entails an in or out folding of a section of sclera in its entire thickness. In 1933 Vogt [161] suggested complete folding of the sclera for cases of detachment complicated by vitreous shrinkage.

Weve [162-167] recommends "reefing" of the sclera by means of a durable material without resecting any of its layers. A meandering suture or a cross stitch of the material is inserted through the superficial layers of the ocular coat over one-third or more of its circumference.

For the purpose of inducing a deeper scleral indentation, Custodis [168-170] places plastic rods underneath inelastic sutures. No scleral resection is performed, and the whole sclera is folded after application of diathermy. The foreign bodies are left in place or purposely removed after two or more weeks.

Everett [157,158] advocates a scleral shortening operation that consists in folding the sclera outward. After the surgery has been completed the folded portion of sclera may or may not be excised. A similar procedure was independently developed by Gayles [171] and Castroviejo.[171-174] The latter employs nonrusting metal clips instead of nonabsorbable surgical (silk) sutures to hold the folded sclera.

For the surgical treatment of retinal detachment associated with staphyloma, Vail [175] inserted mattress sutures passed through the staphyloma which, on being tied, result in a tuck of the sclera that is then excised. The idea was first suggested by Morgan.[176] In a case of retinal detachment associated with scleral staphyloma, Young [177] performed an inward buckling of the staphyloma that resulted in satisfactory reattachment of the retina.

Experimental Study

The assessment of the effects on the choroid induced by mechanical distortion through scleral folding was undertaken because of the surgical significance that the procedure has acquired in the treatment of retinal detachment. In addition, observations were also made on the other ocular coats after the surgical intervention.

Procedure.—Lamellar scleral resections were performed in albino rabbits in an attempt to study the effect of the operation on the ocular coats. The animals were divided into six groups according to postoperative observation periods of one day, three days, five days, seven days, two weeks, and two months. Records were kept listing

the ophthalmoscopic picture of the fundus and the biomicroscopic appearance through dehydrated sclerae.

I. Surgical Technique of Scleral Folding: 1. First stage, exposing the sclera. (*a*) The nictitating membrane was dissected. (*b*) An incision was made in the conjunctiva and Tenon's capsule in the medial portion of the cul-de-sac. (*c*) The conjunctiva was dissected from the sclera back to the limbus in the area between the medial, superior, and inferior vortex veins. (*d*) The necessary muscle fibers were cut close to their insertion when they interfered with exposure.

2. Second stage, resection of the sclera. (*a*) A strip of sclera was outlined with a Lundsgaard knife. The anterior edge of the strip was placed about 5 to 6 mm. from the limbus. It extended between the two nasal vortex veins, and its midportion crossed above the long and short posterior ciliary arteries. The width of the strip was from 1.5 to 2 mm. (*b*) The superficial layers of the sclera were incised, and dissection of the lamellar scleral strip was started at one of its pointed ends. Lean strips of scleral tissue were usually obtained, owing to the relative thinness of the rabbit's sclerotic. Dissection had to be performed very carefully to avoid perforation, particularly at the level of the long posterior ciliary vessels.

3. Third stage, closure of the scleral gap. (*a*) Sutures (0000 black silk) were then inserted through the scleral edges of the resected strip. Two alternate suturing methods were tried, either interrupted or in mattress form. In a third group of animals a polyethylene tube was passed beneath the sutures and buried in the bed of the resection at the time of closure. (*b*) The intraocular pressure was lowered by releasing aqueous humor through a knife-needle puncture in the cornea. (*c*) After the globe softened the approximation of the dissected scleral edges and the infolding of the thin floor were easily achieved by tying the sutures. (*d*) The conjunctival incision was closed with a running suture or interrupted sutures.

II. Linear Indentation: To permit a better visualization of the choroidal vessels underneath the depressed sclera, a linear indentation was produced in the eyes of some animals. This was accomplished by tightly pressing a suture parallel to the equator of the proptosed eye. The maneuver was performed while the vessels were observed through the microscope.

III. Circular Strangulation: In a third group of animals a circular strangulation of the eyeball was produced by a constricting purse-string suture of braided silk. The operation consisted in dissecting the conjunctiva of the upper half of the eye. A silk suture (000) was attached to one of the free quadrants of the globe either by direct suturing or with a fine silk stitch. The circular tie was passed successively underneath the different extraocular muscles. The conjunctiva was sectioned at different points, and the suture was fixed to the superficial layers of the sclera at a constant distance from the limbus. When finally the suture returned to its point of origin the two ends were strongly tied. Burton [178] followed a similar technique, using stainless steel wire, to produce an increase in the length of the anteroposterior diameter of the eyes.

To obtain a better indentation the intraocular pressure was reduced either by puncturing the anterior chamber or by permitting the escape of vitreous through a scleral incision that was later closed.

Observations.—1. Microscopic Findings: (*a*) Sclerotic. Shortly after the operation (24 hours) there was a tendency for the edges of the resected area to separate. This was manifested by the development of "tension lines" around the insertion points of the sutures (Fig. 1). Eventually, the sutures pull through one edge of the resected scleral strip and remain attached to the opposite side (Figs. 2 and 3). From the surgical protocols it was apparent that the time required for the sutures to pull through the

Fig. 1.—Photograph and interpretative drawing: lamellar scleral resection. In all pictures illustrating this type of surgery the cornea of the eye is directed upward and the posterior pole toward the bottom of the page. Original magnification × 10. One day after surgery. Interrupted silk sutures. In the photograph the invaginated area of sclera is not seen, owing to superimposition of layers. The accurate approximation of the scleral edges is manifested by the orderly position of the sutures. Under the scleral buckle the choroidal vessels are not seen, and around it they have a normal appearance. In the drawing "tension lines" have been represented around the insertion points of the sutures. The course of the vessels under the buckle is also shown. At the extreme right there is a schematic cross section of the ocular layers in the operated-on site.

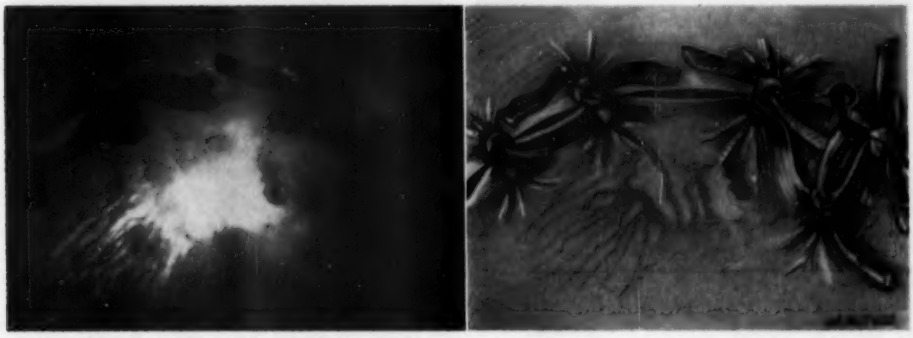

Fig. 2.—Photograph and interpretative drawing: lamellar scleral resection. Original magnification × 10. Three days after surgery. Interrupted silk sutures. In the photograph one of the sutures is "out of line" because it has pulled through one of the edges of the resected area and remains attached to the opposite side. These changes are clearly represented in the diagram.

scleral edges was proportional to the thickness of the sclera included in the suture bite. Between one and two weeks after surgery the scleral fold had disappeared and the resected area had a bluish discoloration with a slightly ectatic appearance (Fig. 4).

Beginning shortly after surgery, the development of a grayish-pink gelatinous tissue was noted on the operated-on region (Fig. 5). The tissue mass enveloped the sutures and eventually attached the conjunctiva firmly to the area of the operation. This episcleral tissue was profusely vascularized, and when it was observed two months after surgery it had the appearance of an intricate meshwork of vessels of a rather large caliber and a tortuous course (Figs. 6 and 8).

The progressive changes previously described follow the same general pattern in the three variant surgical techniques employed. Unfolding of the sclera occurred earlier when interrupted sutures were used to close the scleral defect; the significance of this finding is dubious because of the relatively small number of operations performed.

Fig. 3.—Lamellar scleral resection; photomicroscopic appearance in living rabbit. Original magnification × 10. Five days after surgery. Interrupted silk sutures. The distribution of the sutures becomes more irregular as the sutures progressively pull through the scleral edges. The concomitant unfolding of the buckle permits a better visualization of the underlying choroidal vessels.

When mattress sutures were inserted, they usually became elongated and acquired an oval shape before pulling through the edges of the sclera (Fig. 7).

Polyethylene tubes appeared to induce initially a severer reaction that subsequently subsided. Eventually the tubes were surrounded by a mass of tissue that formed an artificial tunnel on the surface of the sclera (Figs. 9 and 10).

(*b*) Choroid. The immediate effect of scleral folding on the choroid was manifested by blanching of vessels underneath the depressed area. The main trunks of the ciliary vessels may show narrowing of their caliber and slowing of the circulation. The arterial spasm may be rather persistent, this favoring the development of stasis with interference of the blood supply distally to it. The previous changes were only visible when a linear indentation was produced on the sclera. Otherwise, when microscopic studies were performed through an area of complete scleral folding, the choroidal vessels were not seen under the buckle. Around it they have a normal appearance which persisted throughout the period of observation (Fig. 1).

When the intraocular pressure was increased as a result of the operation, modifications in the speed and direction of blood flow occurred in the rest of the choroid. These changes were rapidly relieved by puncturing the anterior chamber.[179] If the eye was undisturbed, the circulatory changes were compensated shortly after surgery, as manifested by normal appearance of flow in observation 24 hours after the operation.

2. Ophthalmoscopic Findings: Examination of the fundus revealed a ridge of retinal

Fig. 4.—Photograph and interpretative drawing: lamellar scleral resection. Original magnification × 10. One week after surgery. Interrupted silk sutures. Almost all sutures have pulled through one of the edges of the resection and remain attached to the opposite side. The buckle of sclera has unfolded, and the bed of the resection has a slightly ectatic appearance, represented in the diagram. The choroidal vessels are not well visualized because of tissue proliferation in the episclera.

Fig. 5.—Lamellar scleral resection: photomicroscopic appearance in living rabbit. Original magnification × 10. Two weeks after surgery. Interrupted silk sutures. In the left portion of the picture there is a mass of tissue that has developed in the episcleral layer surrounding the sutures and that interferes with visualization of deeper structures. In the right-hand side of the picture the layer of tissue has been removed and the choroidal vessels are seen under the dehydrated unfolded sclera.

Fig. 6.—Lamellar scleral resection: photomicrographic appearance in living rabbit. Original magnification × 10. Two months after surgery. Interrupted silk sutures. The sutures have been removed, and the episcleral tissue shows its profuse vascularization. This appears superimposed to the choroidal vessels.

elevation in the area of scleral resection. In this segment, the retina had a grayish-white color, with a slightly undulated surface, the boundaries of which sometimes extended beyond the limits of the resected sclera. In subsequent observations a progressive flattening was noticed that followed approximately the stages of scleral unfolding.

Hemorrhages and other complications due to surgery could be followed easily in the fundus picture.

Comment.—From the previous observations it is evident that lamellar sclera resections under the present experimental conditions produced only a transitory fold-

Fig. 7.—Photograph and interpretative drawing: lamellar scleral resection. Original magnification × 10. Five days after surgery. Mattress silk sutures. This type of suture became elongated and acquired an oval shape before pulling through the edges of the sclera.

Fig. 8.—Lamellar scleral resection: photomicroscopic appearance in living rabbit. Original magnification × 10. Two months after surgery. Mattress silk sutures. A mass of episcleral tissue has developed at the site of the operation. In the upper portion of the picture it completely envelopes the sutures that appear as black patches. The profuse vascularity of this tissue is seen below, where it thins out.

Fig. 9.—Lamellar scleral resection: photomicrographic appearance in living rabbit. Original magnification × 10. Five days after surgery. Interrupted silk sutures. A polyethylene tube was buried in the bed of the resection at the time of the closure.

ing of the sclera. This appears to indicate that a factor in the beneficial effect of the operation is the transient approximation of the external ocular coats to the detached retina. It is possible that the temporary contact of the ocular coats and its accompanying inflammatory reaction (due particularly to the diathermy employed during surgery) will induce an adherence that behaves as an artificial ora serrata. This area will form a limiting boundary in the retina. Behind it the inner ocular coat remains attached if no breaks are present, and in front of it the detached part of the retina

Fig. 10.—Photograph and interpretative drawing: lamellar scleral resection. Original magnification × 10. One week after surgery. Interrupted silk sutures. A suture has pulled through one of the edges of the resected area, and the polyethylene tube originally buried is visualized.

remains circumscribed and unable to extend even if no reattachment occurs.

After the retinal adhesions have acquired sufficient strength, the unfolding of the sclera will not have deleterious effects except for the possibility of the development of an ectatic area in the previously resected sclera. The weakened scleral tissue is at least partially reinforced by the episcleral reaction that develops in the operated-on region.

An anterior binding of the retina can be produced artificially in the entire circumference of the globe. This has been accomplished in clinical practice by a single or by repeated scleral resections. In this procedure the majority of the retinal breaks, usually located between the ora serrata and the equator, are isolated and the spreading of the consecutive detachment of the retina towards the posterior pole of the globe is prevented.

Following the previous considerations, we decided to produce an equatorial strangulation of the globe by means of a tight circular suture. This was easily accomplished and it induced a complete folding of the sclera in the whole circumference of the eye. In some of the operated-on animals degenerative changes occurred in the anterior segment of the eye. These consisted in edema and opacification of the cornea, with increase in thickness and ultimate development of progressive neovascularization. The pupil dilated after surgery, and the blood vessels of the iris became grossly congested; the whole structure had a cyanotic appearance; later, it became pale and atrophic. Also seen were flare and hemorrhages in the anterior chamber and lens opacifications. Ultimately phthisis bulbi developed. The changes described can be explained on the basis of the severe interference with the arterial supply and venous drainage of the affected structures.[179]

In one of the experimental animals that tolerated the intervention rather well, with only mild anterior segment changes, the circular suture eroded through the sclera and was seen in the vitreous cavity in about one-third of its circumference while the rest of the suture remained on the outer surface of the sclera. Some reservation remains as to the behavior of the human eye under similar conditions, this in view of the anatomical differences existing in the ocular circulation of the human and rabbit eyes, mainly the absence of anterior ciliary arteries in the latter.[1,180]

Nevertheless, it would be safer to assume from the previous results that the performance of a scleral resection in the whole circumference of the globe should preferably be done in stages so as to allow sufficient time for the development of a circulatory adaptation.

Summary.—Lamellar scleral resections were performed in albino rabbits, and their progress was followed by microscopic and ophthalmoscopic observations.

Unfolding of the resected sclera occurred in one to two weeks after surgery.

Local and general changes of a transitory nature were observed in the choroidal circulation.

Temporary detachment of the retina occurred in the resected area.

A factor in the beneficial effects of the operation is believed to be due to transitory approximation of the external ocular coats to the detached retina.

A circular strangulation of the globe was produced, and the results obtained are discussed.

Thermal Agents: Diathermy

The biological effect upon the tissues exerted by high-frequency oscillations known clinically as diathermy depends on their absorption by the histological structures. When traversing the body, the energy of the radiations is dissipated in the tissues by the resistance that they offer to the to-and-fro surge of the charge. The oscillations used in diathermy carry sufficient energy to generate heat in such quantity as to produce a significant thermal effect, and the frequency of the current is greater than those frequencies which evoke a neuromuscular response.

The thermal lesion is initially characterized by physiologic stimulation manifested through induction and maintenance of active vasodilatation, cellular proliferations, and acceleration of vital activities; this occurs when a relatively weak current diffuses through a large tissue area and is known as "medical diathermy." Eventually, when the thermal stimulus reaches a critical temperature, it induces tissue death with morphological changes; this results when the heat becomes concentrated near a relatively small electrode and is known as "surgical diathermy." In the following, reference will be made only to the latter type of thermal lesions.

Electrodesiccation occurs if the heat is moderately intense, resulting in a dehydrative effect by gradual evaporation of the tissue fluid, whereby the surface layers are dried and shrunk. Electrocoagulation is produced by a more intense and penetrating current which causes the tissue to be cooked in its own serum with a negligible amount of evaporation. Electrosection (or electrocutting) is accomplished with a highly concentrated current; its effect is the disintegration of the tissues wherever they come in contact with the electrode, while little heat injury affects the surrounding tissues.

The technique of electrosurgery can be monoterminal or biterminal. In monoterminal application a single electrode is employed from which the current spreads in all directions, with the patient's body acting somewhat like a condenser. In biterminal application one electrode is large and the other small, the current tends to flow from one electrode to the other along the lines of least impedance. The intensity of the current is greater close to that electrode which has the smaller area of tissue contact and is known as the "active electrode." There are biterminal techniques in which two small electrodes are applied close together and the spread of current and induction of heat takes place only in the tissues between them.

High-frequency diathermy currents have been generated by two methods: spark-gap generators and vacuum-tube oscillators.

Spark-gap generated current is characterized by being intermittent, damped, of relatively low frequency, and of relatively long wavelength.

Vacuum-tube generated current has allowed the employment of shorter waves with a higher energy content. The flow of this current is constant and undamped, of relatively high or ultrahigh frequency with relatively short wavelength.[181-183]

Diathermy-induced pathological changes are easily accomplished in the eyes of experimental animals. The literature on these effects can be represented by the works of Sauls,[184] Jess,[185] Mayer,[186] Arruga,[187] Coppez,[188-190] von Szily and Machemer,[191] Campos,[192] Bucallosi,[193] Weekers,[194,195] Bessiere and Bruel,[196] Pischel,[197] Scheie and Jerome,[25] and Swan and Christensen.[183]

The therapeutic value of diathermy in ocular surgery has been found primarily in the treatment of serous retinal detachment (retinopexy) and with less encouraging results in glaucoma (cyclodiathermy). Brief reference will be made to both procedures.

A. Retinopexy.—The use of diathermy for the treatment of retinal detachment attempts to excite an exudative choroidal reaction over the region of the break. This is subsequently followed by evacuation of the subretinal fluid so that the edges of the break will touch the area of choroiditis.

In the technique of diathermy operations three different active electrodes are employed. They are frequently combined, and numerous variations of technical details have been described.

1. Surface Diathermy: Originally recommended by Weve[198,199] and Larsson,[200-202] this technique has been followed by many others. Surface coagulation is applied by dull electrodes of various forms and sizes. The advantages of surface diathermy are that the field is kept dry, the eyeball is kept firm, and the application of the electrodes is easy. Disadvantages are the uncertainty

of transcleral dosage and, when it is used exclusively, the difficulty in draining subretinal fluid.[22] For scleral shrinkage the fields should be moist to obtain maximum effect.[203]

2. Partial Penetrating Diathermy: For this operative routine the Lindner, Pischel,[197] or other similar electrodes, usually with a short 0.5 mm. point, are used. In some cases, as when the sclera is thickened by scar tissue, electrodes with longer points, such as 1.0 or 1.5 mm. may be needed. The advantages of this type of diathermy are that the field is dry and that the small point entering the sclera avoids sliding around of the electrode with dissipation of current; it also carries the current through the sclera and closer to the choroid, where the exudative reaction will be produced.[22]

3. Perforating Diathermy: This technique was evolved by Weve [204-206] and Safar [207-209] and provides many fine openings for drainage of the subretinal fluid. For this purpose a number of electrodes and pins have been designed. They include the various needles of Safar,[207-209] Walker,[210-212] and others—some single-pointed and others with multiple points, some curved and others straight, to be applied either by means of a holding forceps or with a stylus. Also in this group can be considered the electrode of Lacarrere [213] that terminates in a small glass tube through which a wire may be projected any desired length, depending upon the degree of penetration which is necessary. The advantage of this technique is the good drainage it provides with little tissue damage or retinal atrophy. The disadvantages are that the eye might get soft, the field is wet, and the retina is injured more as the subretinal fluid escapes.[22] The loss of fluid during operation offers no disadvantage, according to some authors.[203]

B. Cyclodiathermy.—Cyclodiathermy as a therapeutic procedure in cases of glaucoma was first employed by Weve [214] and particularly advocated by Vogt.[215-220] Since its introduction, every possible combination of cyclodiathermy has been attempted, and the interventions vary widely as to topography of application and details of surgical technique.

In regard to site, Vogt [215-216] first suggested diathermy punctures over the ciliary body in a band circumscribed between 1.5 and 3.5 mm. from the limbus. Because of complications resulting from this procedure, this author [217-220] later advised that the punctures not come closer than 2 to 2.5 mm. from the cornea. Since this early description the limbal distance at which the operation is performed has been subjected to variations showing a general tendency toward a backward displacement. The distance from the limbus at which diathermy is applied has been given at 2 mm. by Redslob [221]; 3 to 5 mm. by Albaugh and Dunphy [222] and Marr [223]; 6 mm. by Castroviejo [224] and Scheie, Frayer, and Spencer [225]; 5 to 7 mm. by Thiel [226] and Desvignes and Naudin [227]; 7 mm. by Verrey [228,229] and Maeder [230]; 7 to 8 mm. by Weekers and Weekers [231-235]; 8 mm. by Arruga [236] and Reiser [237,238]; 7 to 9 mm. by Urrets-Zavalia and Urrets-Zavalia,[239,240] and 6 up to 11 mm. by Forbes.[241,242]

The transconjunctival approach was recommended by Weekers and Weekers,[231-235] Redslob,[221] Desvignes and Naudin,[227] Verrey,[228,229] Arruga,[236] Castroviejo,[224] Urrets-Zavalia and Urrets-Zavalia,[239,240] Maeder,[230] Scheie, Frayer, and Spencer,[225] and others, while Vogt,[215-220] Albaugh and Dunphy,[222] Meyer,[243,244] Marr,[223] Reiser,[237, 238] Forbes,[241,242] and others used diathermic applications over the previously denuded sclera. Thiel [226] and Diaz-Dominguez [245] proposed a subscleral method to concentrate better the coagulating action over the ciliary body.

In the original procedure of Vogt [215-220] the operation was performed over an area covering one-third to one-half the circumference of the globe. Albaugh and Dunphy,[222] Marr,[223] Reiser,[237,238] and others apply the electrode over one-half the global circumference. Weekers and Weekers,[231-235] Redslob,[221] Desvignes and Naudin,[227]

Verrey,[228,229] Urrets-Zavalia and Urrets-Zavalia,[239,240] Maeder,[230] and others tried to encircle the limbus in its entirety by diathermic applications in all quadrants. While Arruga[236] avoids the anterior ciliary vessels, Forbes[241,242] and Scheie, Frayer, and Spencer[225] purposely attempt their obliteration.

Vogt[217-220] recommended as many as 100 diathermic punctures, while Redslob[221] and Desvignes and Naudin[227] used eight applications in their average procedure. Within these two extremes a wide range of number of applications has been advocated by different authors: Forbes,[241,242] 50 to 30; Marr,[223] 40 to 30; Verrey,[228,229] 20 to 18; Arruga,[236] 20 to 15; Weekers and Weekers,[231-235] and Urrets-Zavalia and Urrets-Zavalia,[239,240] 20 to 12; Goldsmith,[246] 16 to 12; Maeder,[230] 12 to 8; Castroviejo[224] and Scheie, Frayer, and Spencer,[225] 10 to 8.

Surface nonperforating cyclodiathermy has been employed by Albaugh and Dunphy,[222] Weekers and Weekers,[231-235] Desvignes and Naudin,[227] Marr,[223] Verrey,[228,229] Reiser,[237,238] Goldsmith,[246] and others. The diameter of the flat electrode used has varied between 2 mm. (Marr) and 0.6 or 0.8 by 1 mm. in size (Weekers and Weekers). The last-mentioned electrode is included in a thermoelectric circuit so that the temperatures can be measured during application (Coppez[247]). In the subscleral technique of Thiel[226] and Diaz-Dominguez[245] an electrode with the shape of a cyclodialysis spatula is employed. Partial penetrating electrodes have been used by Vogt,[217,220] Meyer,[243,244] Marr,[223] Philip,[248] and others. Perforating diathermy was advocated by Vogt[215,216]; Redslob[221]; Arruga[236]; Castroviejo[227]; Scheie, Frayer, and Spencer,[225] and others, who considered the loss of small amounts of fluid as harmless and even helpful in the prevention of secondary rises.

Time of application for each diathermy point also shows variability. This is attested in the following list of times recommended by different authors: 0.5 to 1.5 seconds by Vogt[215-220]; 1 to 2 seconds by Redslob[221]; 2 to 4 seconds by Forbes[241,242]; 1 to 5 seconds by Marr[223]; 6 to 8 seconds by Goldsmith[246]; 8 to 10 seconds by Albaugh and Dunphy[222]; 10 seconds by Desvignes and Naudin,[227] Reiser,[237,238] Maeder,[230] and Scheie, Frayer, and Spencer[225]; 10 to 15 seconds by Verrey[228,229]; 15 seconds by Weekers and Weekers[231,235] and Urrets-Zavalia and Urrets-Zavalia.[239,240]

Experimental Study

Method.—Transconjunctival coagulating points were applied with a blunt-tipped electrode of 0.5 mm. in diameter. The apparatus employed was a Thermosector † that provided the necessary coagulating current.

The eyes of the experimental animals were proptosed, and the electrode was applied usually only for a few seconds—the time required to obtain a complete blanching of the vascularity of the area without perforating the globe. Isolated points or clusters were applied along the larger choroidal vessels or in the midchoroidal area.

Microscopic observations of the prepared animals were made at weekly intervals for a period of four months.

Observations.—After application of diathermy to the surface of the sclera the point of coagulation showed three poorly outlined concentric zones (Fig. 11).

(*a*) The center of the lesion had a granular gray-pearly appearance, was avascular, and in isolated sites showed areas of blood stasis in the choroid. The granular appearance of the lesion progressively disappeared, and it acquired a uniform transparent aspect 12 weeks after surgery.

(*b*) The intermediate zone is characterized by a lack of active circulation and the presence of numerous areas of stasis in the choroidal vessels. These slowly disappeared and were not present six weeks after the original procedure.

† This unit has a vacuum-tube oscillator that generates an undamped, constant current with a frequency that averages approximately 22,000,000 cps and has a wavelength of about 17 meters.

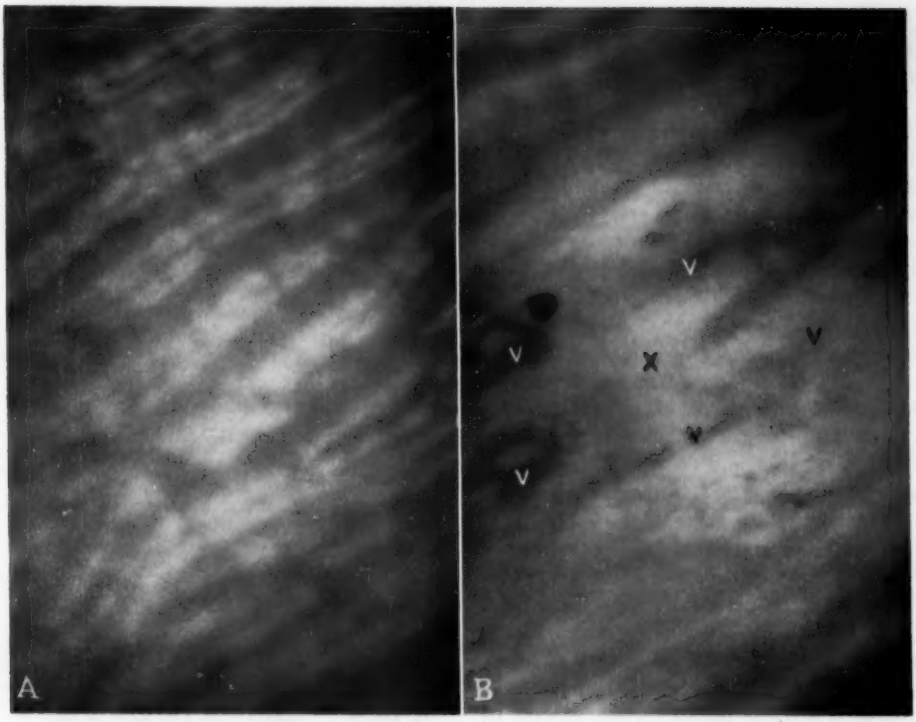

Fig. 11.—Effect of diathermy on the choroidal vessels. Original magnification × 40. *A*, photomicrograph showing the normal appearance of the vessels in the midchoroidal area. *B*, the same area as in the previous picture after application of a diathermy point. Note the lack of vascularity in the center of the lesion (*X*). This is surrounded by areas of circulatory stasis (*V*), where the vessels appear darker, thinner, and with an irregular caliber.

One week after the diathermic application there was in the intermediate zone evidence of circulation in vessels of extremely small caliber. The active motion of blood became more and more apparent with time. The vessels visualized had the appearance of terminal arterioles and collecting venules [1] that averaged 25μ in diameter at the end of this study.

The small vessels visualized in the intermediate zone had a directional arrangement similar to that in the rest of the choroid. At the periphery the small vessels drained into the surrounding larger channels. The central end of these vessels encroached for a variable distance into the center of the coagulation point, that remained as the most poorly vascularized area.

The direction of flow in the venules is centrifugal—from the center of the lesion into the larger vessels of the periphery. As a result, the movement of blood at some points is opposite to the one present under normal circumstances. The motion of blood in the terminal arterioles appears to end in or about the center of the lesion, but its final destiny could not be followed.

(*c*) In the periphery of the diathermy point all the affected veins and arterioles in the choroid rearranged the direction of their blood flow into neighboring vessels through all the available anastomoses. On some occasions the column of blood undergoes a complete reversal in its direction; on others the deviation is minimal, but, whatever the arrangement, the blood rapidly follows the normal direction of flow that prevails in the unaffected surrounding areas. These modifications persisted throughout the observation period. Changes in direction of blood

flow after obliteration of vessels feeding and draining the choroid have been previously described.[179]

In some diathermy points larger choroidal vessels were seen to traverse the lesion, usually at its periphery. These vessels showed a direct continuity with the surrounding channels; in general, their caliber was narrowed at the point of entrance into the lesion and acquired a larger diameter when leaving the diathermy point. On occasion the course of the vessels became tortuous on crossing the lesion. The direction of blood flow maintained its normal characteristics. The larger vessels were less numerous at the points of coagulation than in the unaffected areas, and occasionally they were seen to terminate or arise from the areas of coagulation.

From comparative studies of different lesions, it was evident that after diathermic application the smaller vessels became obliterated while larger channels had a greater tendency to remain patent.

When multiple diathermic points were produced in close proximity the process of revascularization was notably less efficient than when lesions were isolated and surrounded by unaffected tissue.

Points of coagulation located near the limbus or closely approximated to each other were more frequently invaded by vessels extending from the episcleral tissues. These vessels were tortuous and branched into intricate irregular patterns.

Comment and Summary.—It is evident from the present studies that after diathermic coagulation of the eye there is a tendency for the lesions to revascularize. This tendency together with the profuse collaterality of the choroidal system would tend to compensate imbalances in the hemodynamics of the eye that develop following the use of diathermy.

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The Agar-Diffusion Technique in Studies of Immunity to Adenoviruses

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Various viral agents of the adenovirus group have now been isolated from cases of epidemic keratoconjunctivitis (EKC),[1,2] pharyngoconjunctival fever,[3] and sporadic forms of catarrhal and follicular conjunctivitis.[4]

For the identification of adenoviruses a soluble complement-fixing antigen, which is specific for the adenovirus group and common to all its members, is used. Serotypes of the adenovirus group are generally determined by type-specific neutralizing antibody tests with use of rabbit immune sera.[3] Eighteen human and five simian serotypes of adenoviruses have now been established by this method.[5]

Precipitation tests in vitro, using vaccinia virus [6] and psittacosis virus [7] as antigens and their respective antisera as sources of antibody, have been performed with success, but viruses of smaller size, with the possible exception of influenza virus,[8] have thus far not proved so satisfactory for this gross type of reaction. Demonstration of precipitating antibody to viruses of smaller size may require some more sensitive method for their detection.

With this in mind, the agar-diffusion technique of Ouchterlony,[9] as modified by Halbert,[10] has been utilized as a new method for demonstrating precipitation reactions with several adenoviruses.

Methods and Materials

Preparation of Agar Plates.—Difco Bacto-agar buffered with barbital (Veronal) was used as the diffusion medium for the demonstration of precipitating antibodies. To a 0.8% solution of melted agar, made up in 0.85% sodium chloride, barbital sodium and aminoacetic acid were added to final concentrations of M/25 and M/20, respectively.[11] The solution was then neutralized by the dropwise addition of concentrated hydrochloric acid to a pH of 7.4. The agar was poured in 25 ml. volumes into separate sterile Petri dishes, allowed to harden at room temperature, and refrigerated at 7 C.

Holes or "wells" were cut out of the agar with sterile cork borers of 5 mm. internal diameter. Six holes were placed in a hexagonal pattern around a central reservoir at a radial distance of 1.3 cm. In antigen screening experiments the hyperimmune rabbit serum was pipetted into the central well and the antigens to be tested were placed in the peripheral wells. In other experiments antigen was placed in the central well and the peripheral wells were filled with human or control animal sera. Agar plates were refrigerated at 7 C and observed daily.

Antigens.—Virus antigens consisted of supernatant fluids from KB-[12] or HeLa-cell cultures * infected with several known adenovirus types. All antigens were concentrated to one-half their original volume by evaporation at 5 C and were inactivated by heating at 56 C for 30 minutes. The Sekiya strain of Type 7, the Segami strain of Type 8, and the prototype strains of Types 3 and 8 were grown in KB-cell cultures, maintained in Eagle's Basal

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* KB cells (derived from human epidermoid carcinoma of the floor of the mouth) and HeLa cells (derived from human cervical carcinoma) were obtained from Microbiological Associates, Inc., Bethesda, Md.

Medium with 5% chicken serum; prototype strains[3,5] of types 1, 2, 5, 6, and 8 were grown in HeLa-cell cultures maintained in Eagle's Basal Medium with 2% horse serum. The Sekiya and Segami strains were isolated during a recent epidemic in Kumamoto, Japan, from conjunctival scrapings of patients with clinical symptoms of epidemic keratoconjunctivitis.[13]

Control antigens consisted of uninfected KB and HeLa cells; ECHO virus (enteric cytopathogenic human orphan virus) Type 11, grown in HeLa cells maintained in Eagle's Basal Medium with 5% horse serum; Toxoplasma gondii,† and β-hemolytic Streptococcus.‡

Antisera.—Prototype adenovirus antisera § (Types 1, 2, 3, 4, 5, 7, 7′, and 8) were obtained from rabbits hyperimmunized by five intravenous injections of 1.5 ml. of supernatant fluid from infected KB cells, maintained in Eagle's Basal Medium with 5% chicken or horse serum, or monkey kidney cells in synthetic medium No. 199 without serum.‖ Human specimens consisted of paired acute and convalescent sera from nine patients with suspected epidemic keratoconjunctivitis and serum from normal adults.

Because the virus pools used to stimulate antibody formation in certain rabbits contained tissue and medium components common to the precipitin test antigens, these rabbit sera were first absorbed with chicken or horse serum and normal HeLa cells. Two volumes of rabbit serum were mixed with one volume of chicken or horse serum and incubated for one hour at 37 C. The mixture was refrigerated overnight at 7 C, and the following day the flocculent precipitate was removed by centrifugation at 1500 rpm for 15 minutes. The absorption procedure was repeated on successive days until no precipitate could be detected.

The serum was absorbed with noninfected HeLa cells as follows: One HeLa-cell tube culture containing about 100,000 cells was centrifuged, and the supernatant fluid was discarded. To the sediment 0.5 cc. of the serum to be absorbed was added. Following agitation, the mixture was incubated for one hour at 37 C. The mixture was then alternately frozen at −20 C and thawed 10 times over a 48-hour period. The sediment was separated from the mixture by centrifuging at 1500 rpm for 15 minutes, and the resultant supernatant was tested for antibody.

Methods of Neutralization Tests and Complement-Fixation Tests.—Virus neutralization tests were performed by a modification of the techniques of Rowe et al.[3] and Jawetz et al.[1] Monkey kidney cell cultures were used as the indicator system. The test results were read 24 hours after the virus control tube first showed severe cytopathic changes. Cytopathic effects were graded on a scale of 0 to 4+. Evidence for neutralization was considered definite only when a difference of 2+ in readings was obtained between the control tubes and the serum tubes for more than two consecutive days.

Complement-fixation tests on these same sera were performed according to the method of Rowe et al.,[3] who provided the data presented in this series.

Results

In a preliminary experiment, illustrated in Figure 1, precipitation lines appeared between adenovirus Type 8 (Segami strain), unabsorbed Type 8 hyperimmune rabbit

† Toxoplasma antigen was prepared from the pooled peritoneal exudate of mice infected with RH strain of T. gondii.

‡ Strain H-414-6, supplied by Dr. Patricia Fitzgerald, Department of Ophthalmology, Columbia University College of Physicians and Surgeons.

§ Samples of rabbit hyperimmune serum, virus pools, and various tissue culture materials were supplied by Dr. Wallace P. Rowe and Miss Janet W. Hartley, Section on Virus and Rickettsial Diseases, National Institute of Allergy and Infectious Diseases, under whose direction the confirmatory complement-fixation tests used in this study were also performed.

‖ Medium No. 199, obtained originally from Microbiological Associates, Bethesda, Md., is a synthetic mixture of amino acids, vitamins, and phenol red, in a balanced salt solution.

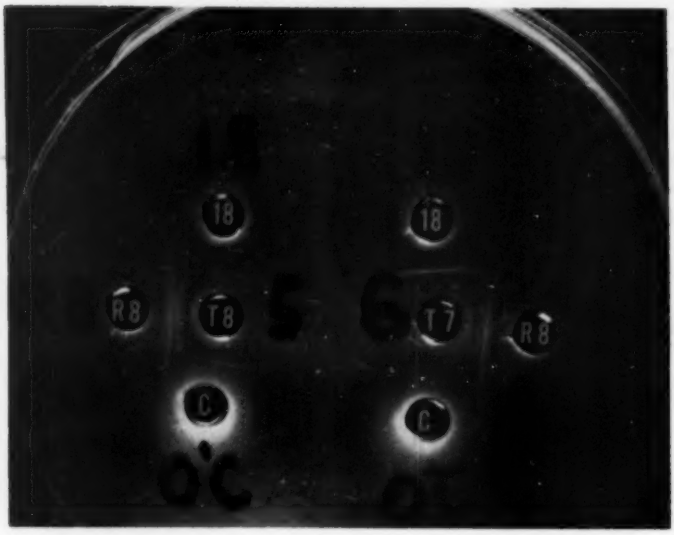

Fig. 1.—*T8*, Segami virus (Type 8); *T7*, Sekiya virus (Type 7); *R8*, rabbit immune serum against Type 8 virus; *18*, convalescent serum of patient with EKC; *C*, "normal" human serum.

serum, and convalescent serum from an EKC patient; an almost identical pattern was observed with the Sekiya strain of Type 7 adenovirus. The lines appeared geometrically straight and at right angles to an imaginary line constructed between the centers of the corresponding antigen and antibody reservoirs. The control serum (O'C), although obtained from an apparently normal volunteer, was later found to have a complement-fixation titer of 1:16 against both Type 3 and Type 8 adenovirus.

In order to determine the specificity of the reactions observed, tests were performed with a number of antigens and hyperimmune antisera, prepared with various cells and media; appropriate control sera and antigens were also tested. The results are presented in Table 1 and are illustrated in Figure 2. No reactions were obtained with absorbed immune rabbit sera tested against normal serum and tissue components, or against cells infected with an unrelated virus, ECHO Type 11. Hyperimmune rabbit sera, monotypic in neutralization tests, were capable of reacting with antigens of a variety of serotypes, but they frequently reacted most strongly with the homologous type.

The parallel lines seen opposite the immune rabbit serum in Figure 1 were interpreted as reflections of multiple antigen-antibody reactions of nonviral components, since after absorption with HeLa cells and chicken serum only one line was formed (Fig. 2). The ends of the precipitin lines formed an obtuse angle with each other, illustrating, according to Ouchterlony's "reaction of identity," the presence of the same antibody moiety in the various reacting couples.

Paired acute and convalescent sera from the donors of the Segami and Sekiya adenovirus isolates were tested against both the homologous and the heterologous virus. The results, compared with the values obtained in complement-fixation and neutralization tests, are presented in Table 2. Definite precipitin lines were seen with all sera (Fig. 3), but in each case the reaction of the acute serum was weaker or slower to appear than that of the convalescent.

Multiple precipitation lines were observed in several human sera. Whether these were reflections of nonspecific reactions or indications of several antigenic components can not yet be explained.

Of interest was the chance observation that a single precipitin line formed between

TABLE 1.—*Degree of Precipitation Obtained with Various Antisera* *

Serum	Immunized with: Adenovirus Type	Immunized with: Culture Medium†	Adenovirus Antigens: Cultivated in KB with Chicken Serum: 3	7 (Sekiya)	8 (Segami)	8	Adenovirus Antigens: Cultivated in HeLa Cells with Horse Serum: 1	2	5	6	8	Control Antigens: ECHO Virus Type 11	Streptococcus	HeLa Cell	Horse Serum	Chicken Serum	Neutralization Test Titers of the Various Antisera Against Adenovirus Types ‡: 1	2	3	4	5	7	8
Rabbit	3	KB	3+	3+	2+	3+	1+	1+	1+	1+	0	0	0	0	0	0	<5	<5	2560	<5		<5	<5
	7	HS	2+	3+	2+	2+	1+	1+	1+	0	0	0					<5	<5	<5	<5	<5	640	<5
	8	HeLa CS	3+	2+	4+	4+		2+			1+	0	0		0	0	<5	<5	<5	<5	<5	<5	>80
	1	MK	3+	3+	2+	2+										0	80						
	2		4+	4+	4+	4+										0		320					
	3		4+	3+	2+	3+						0							160				
	4		3+	3+	3+	3+						0								>640			
	5		1+	1+	1+	1+						0				0					>80 but <320		
	7		1+	3+	1+	1+						0				0						320	
Horse			0	0	0	0	0	0		0	0	0	0	0									
Chicken			0		0							0	0	0									
Rabbit			0		0	0							0										
Toxoplasma antigen No. 1			1+	1+	1+	1+						0	0	0	0	0							
Toxoplasma antigen No. 2			0	0	0	0						0		0	0	0							
Complement fixation titer of adenovirus used			>32	>32	>32	>32	64	32	32	16	<8												

* The amount or precipitation in the precipitin lines is graded according to a system of 1+ to 4+.
† KB = KB cells; HeLa, HeLa cells; HS, horse serum; CS, chicken serum; MK, monkey kidney cell culture without serum.
‡ Titer represents reciprocal of serum dilution.
§ Underlined figures represent homologous antibody antigen reaction.

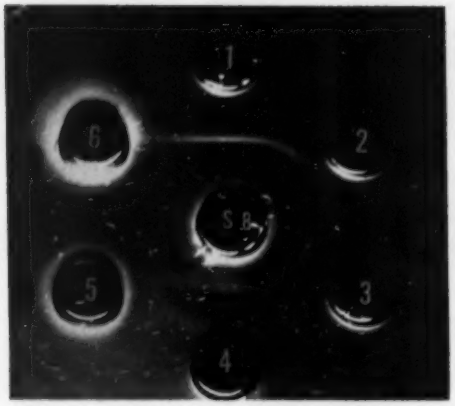

Fig. 2.—*S8*, rabbit immune serum against Type 8 virus, absorbed with chicken serum; *1*, Segami virus (Type 8); *2*, Type 8 virus; *3*, Type 3 virus; *4*, Sekiya virus (Type 7); *5*, horse serum; *6*, chicken serum No. 1.

the Toxoplasma antigen well and the Segami antigen pool. In subsequent tests this lot of antigen (No. 1) showed a similar pattern when tested against adenovirus Types 3, 7, and 8; it was strongly anticomplementary at a dilution of 1:16. Another Toxoplasma antigen (No. 2) showed no precipitin line formation.

Comment

The precipitating antibodies demonstrated by the agar-diffusion technique appear to be specific for the adenovirus group. Heterologous reactions similar to those occurring in the complement-fixation test[3] were obtained when monotypic hyperimmune rabbit sera were tested against various adenovirus antigens; conversely, these antigens were useful for demonstrating precipitating antibody in rabbit immune sera prepared against a number of adenovirus types. However, the occurrence of stronger reactions in homologous systems was relatively consistent.

The presence of precipitating antibody in paired sera from patients with EKC could be detected with Type 8 virus antigen. Precipitin lines in sera from the acute phase of the disease were weaker and later in appearance than those seen opposite the convalescent serum, demonstrating some correlation between the presence of precipitating antibodies and complement-fixing and neutralizing antibodies during various phases of disease.

Although this procedure would appear to have no advantages over the complement-fixation and neutralization tests as a routine diagnostic or virus-typing method, when combined with careful absorption procedures it might serve as a convenient system for demonstrating and delineating the antigenic

TABLE 2.—*Degree of Precipitation from Serum of Patients with EKC*

Patients' Sera		Segami Virus (Type 8)		Sekiya Virus (Type 7)		Complement-Fixing Titer*	Neutralizing Antibody Titer			
		Degree of Precipitation	Time of Appearance, Hr.	Degree of Precipitation	Time of Appearance, Hr.	Type 8	Type 1	Segami	Trim †	Sekiya
1 (Segami)	acute	3+	48	3+	48		< 8	< 5		>10
	conv.	4+	24	4+	24		16	20		20
2 (Sekiya)	acute	1+	72	2+	72	16	16	<10		<10
	conv.	3+, 1+*	48, 120	5+	36	32	64	<10		80
3	acute	1+	72			< 8	16	<10		<10
	conv.	3+	24			32	64	40		<10
4	acute	0				< 8	< 8	<10		<10
	conv.	2+	24			16	< 8	80		<10
5	acute	1+	48			< 8	< 8	< 5	< 5	<10
	conv.	3+	48			< 8	64	40	40	<10
6	acute	1+	96			< 8	< 8	<10		<10
	conv.	2+	96			< 8	16	>40		<10
7	acute	1+	96				8		< 5	
	conv.	3+	48				16		20	
8	acute	3+, 2+	48, 72				< 8		<10	<10
	conv.	2+, 4+, 3+	72, 48, 72				64		40	<10
9	acute	0					8		< 5	
	conv.	3+, 3+, 4+	96, 48, 24				64		40	
10	conv.	3+, 3+, 4+	120, 72, 24				64		40	
11	normal	3+	48			< 8				
12	normal	2+	72			< 8				
13	normal	0								

* When multiple bands were observed, they were graded in intensity according to a scale of 1+ to 4+. In each case the first digit refers to the band closest to the antigen well. The other digits represent successive lines, reading in order from the antigen well to the antibody well.

† Trim virus is the prototype of adenovirus Type 8, first described by Jawetz, et al.[1]

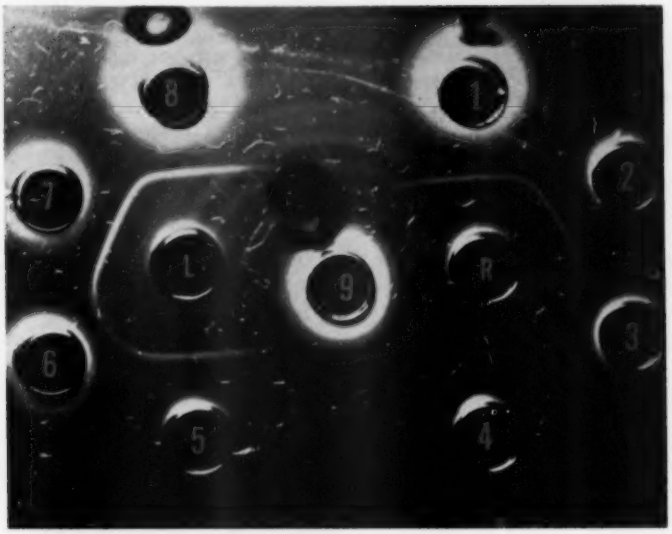

Fig. 3.—Central wells: *R*, Segami virus; *L*, Sekiya virus. Peripheral wells: *1* and *8*, Segami serum (acute phase); *2* and *7*, Segami serum (convalescent phase); *3* and *6*, Sekiya serum (acute); *4* and *5*, Sekiya serum (convalescent); *9*, normal human serum.

composition of individual types. Included in Table 2 are the results of tests of additional paired sera from patients with EKC tested by precipitation, complement-fixation, and neutralization. The reaction patterns in precipitation tests most closely paralleled those of the group-specific complement-fixation test.

Summary

Precipitating antibodies against adenoviruses Types 1, 2, 3, 5, 6, 7, and 8 have been demonstrated by an agar-diffusion technique.

The antibodies detected by this method appear to be group-specific.

With use of adenovirus antigens, increases in precipitating antibody can be demonstrated in paired sera from patients with clinical epidemic keratoconjunctivitis.

Dr. Wallace P. Rowe, of the National Institute of Allergy and Infectious Diseases, gave guidance and constructive criticism, and Miss J. W. Hartley and Mr. H. C. Turner, of the same Institute, assisted in the study. Dr. G. R. O'Connor, of the National Institute of Neurological Diseases and Blindness, and Dr. Yukihiko Mitsui, of Kumamoto University Medical College, also gave assistance and advice. Mr. Lee Caldwell gave technical assistance.

Ophthalmology Branch, National Institute of Neurological Diseases and Blindness (14).

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Eosinophilic Granuloma of the Orbit

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Eosinophilic granuloma of the bone is a rare disease. It was described by Froser in 1935 and later on by Litchenstein and Jaffe [6] in 1940. Children and young adults are most often affected. General health is unimpaired. Sometimes there is low-grade pyrexia, but usually there is absence of any systemic disturbance. The lesions are situated in the flat bones, e. g., ribs, pelvis, or skull. Occasionally the long bones show the deposits. In fact, any bone, with the possible exception of those of the hand and feet, may be involved. The affected bone is rarefied, and its shell is expanded. The lesions are moderately tender; there is slight or dull pain. When the affected bone is in the vicinity of a joint, its movements are restricted. Involvement of liver, spleen, and cerebral structures has also been reported.

Exophthalmos produced by an eosinophilic granulomatous lesion in the orbit is a very rare occurrence. Truhlsen [7] reported a case of exophthalmos due to eosinophilic granuloma. Reviewing its reported incidence, he mentions only four references. Wheeler [8] described a case of a 34-year-old man with exophthalmos. Gross and Jacox [4] mentioned another case. Beller and Kronbleuth [1] published two cases. Fralick,[2] in the annual review of orbit and its diseases, referred to three articles on eosinophilic granuloma in the non-English literature. The following case report adds another to this small series.

Report of a Case

A 7-year-old boy, coming from a submountainous district of Punjab, India, was admitted to the R. L. Eye and Ear, Nose, and Throat Hospital, Amritsar, on May 23, 1956, with proptosed right eye, a soft swelling over the back of the head, and pain in the right shoulder, of six months' duration.

The onset was insidious. The father noticed that the right eye was becoming prominent and that there was a soft swelling about the size of an almond over the back of the head. Both the eye and the head swelling progressively increased. Two months later the child started complaining of pain at the back of the right shoulder. Its movements were limited. There was no systemic disturbance and no impairment of vision, diplopia, headache, vomiting, cough, or urinary complaints.

The patient was born prematurely and was the seventh in birth order. He had thrived satisfactorily till the age of 3, when he suffered discharging ears which continued intermittently for three years. There were six deaths of other siblings in the family; four of these were during infancy from miscellaneous causes such as diarrheas, vomiting, wasting, and tuberculosis. There is only one other living brother, aged 15 years. There is nothing else of significance in development and social history.

Physical Examination.—The patient was well built and moderately well nourished except for slight anemia. Weight, 36 lb.; height, 43 in. (106 cm.); skull circumference, 49 cm.

On the scalp, at the lambdal region, there was a soft fluctuant oval swelling about 3 cm. in diameter (Fig. 1). It was somewhat tender. The overlying skin was normal. A similar but smaller swelling 1.5 cm. in diameter was also present a little below and behind the former swelling. The right eye

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Fig. 1.—Photograph showing a nodule at the parieto-occipital junction.

(Fig. 2) showed axial exophthalmos of 6 mm. There was no other abnormality of the eye, neurological or muscular. All the movements of the eyeball were free. Vision was 6/6 J-1, and the fundi were normal. Palpation below the superior orbital margin revealed a firm mass ½ in. (1.25 cm.) behind it. There was bilateral central perforation of the ear drums, without any granulation tissue but with serous discharge.

The right supraspinous fossa was full and tender to touch. There was difficulty in abduction, more than 90 degrees of which was not possible. There was severe pain over the supraspinous fossa when manipulation of the shoulder was attempted.

Fig. 2.—Photograph showing exophthalmos of the right eye.

There was no abnormality in the respiratory, cardiovascular, digestive, lymphatic, nervous, or other systems.

Investigations.—Blood studies showed hemoglobin, 9 gm.; RBC, 4,500,000 per cubic millimeter; total leukocyte count, 15,500 per cubic millimeter, with polymorphonuclear cells 63%, lymphocytes 32%, eosinophils 4%, and monocytes 1%; sedimentation rate (first hour, Westergren), 4 mm.; serum proteins, 5.6 mg. per 100 cc.; serum cholesterol, 86 mg. per 100 cc.; VDRL and Kahn tests, negative; cerebrospinal fluid, no abnormality; Mantoux test, positive in 1:1000 dilution. Urine and stools showed no abnormality; there was no Bence Jones protein.

Skiagrams of the skull, orbit, and shoulder joint showed multiple bony defects of an irregular size and shape, without any reactive change in the surrounding bone (Figs. 3 to 7).

Fig. 3.—Skiagram showing a rarefying lesion in the right orbital apex.

Fig. 4.—Skiagram showing a large "punched out" defect in the occipital bone.

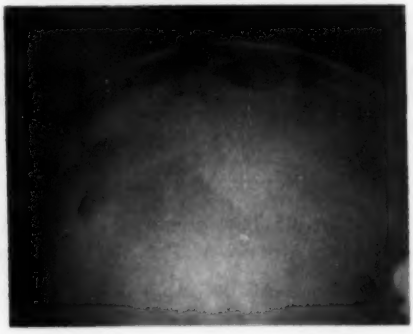


Fig. 5.—Skiagram showing multiple bony defects in the posterior skull.

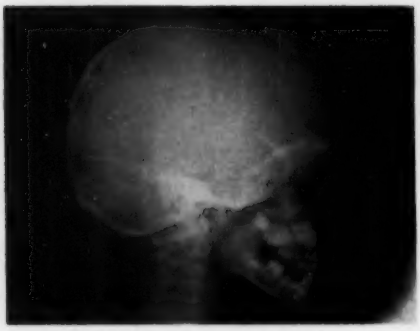


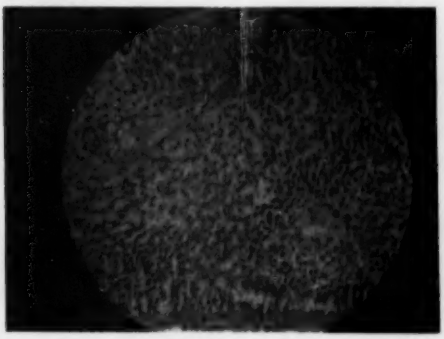
Fig. 6.—Skiagram. Laternal view of skull, showing multiple bony defects.

Biopsy of tissue removed from the lambdal swelling revealed small pieces of soft light brown granular mass. Histopathologic study showed a large number of cells with indistinct cytoplasmic margins and an ovoid or irregular rounded nucleus, with chromatin irregularly scattered but mostly concentrated at the periphery. There was vacuolation of the cytoplasm in many cells and diffuse infiltration with mature eosinophils. At certain places the infiltration was very dense. There were a few multinucleated giant cells with three or four nuclei. Blood vessels were well formed (Fig. 8).

Diagnosis.—This patient was labeled in the outpatient clinic as a case of exophthalmos due probably to orbital tuberculoma, a condition that has been found to be a fairly frequent cause of exophthalmos in this part of the country. The investigations, however, precluded this diagnosis. The multiple large bony defects seen on radiological examination of the skull, scapula, and orbit suggested the rare possibility of multiple myeloma occurring at this age or secondary deposits from a primary malignant growth, such as neuroblastoma of the adrenals or somewhere else in the body, or Hand-Schüller-Christian disease. The few investigations carried out, however, did not substantiate any one of these diagnoses.

Fig. 7.—Right shoulder. Skiagram showing an area of rarefaction in the right scapula.

Fig. 8.—Photomicrograph showing mature eosinophils, a few multinucleated giant cells, and round cells.



The heavy preponderance of eosinophilic leucocytes found on histopathological study gave a clue to the true diagnosis.

Course.—The lambdal swelling, which was curetted, entirely disappeared after a month. The supraspinous fossa was explored, and light-pink-colored granulation tissue, soft in consistency, was curetted out. The patient was kept under observation for four months. During this period, the right shoulder joint showed a greater range of movement.

A course of deep x-ray therapy for the orbit was proposed but not carried out.

Comment

The typical histopathological picture leaves no doubt about the diagnosis.

In retrospect the clinical history was typical, a slow insidious onset of nodular swelling in various parts of the body, orbit, scalp, and scapula, with bilateral ear discharge, without much-impaired general health. There was no evidence of diabetes insipidus. Except for the typical histopathological picture revealed by biopsy and the bony defects found on roentgen study, all other investigations were negative.

Eosinophilic granuloma has been correlated with Letterer-Siwe disease and with Hand-Schüller-Christian disease, all granulomatous disorders of the reticuloendothelial system. Lesions in eosinophilic granuloma may occur in any bone, usually those of skull, pelvis, vertebrae, ribs, or long bones. In this case the scapula was also involved. This has not been reported in the literature. The lesion is a granulomatous tumor which is soft, friable, and yellowish brown or pinkish buff; there may be areas of necrosis and hemorrhages. The affected area of the bone is destroyed, but when healing occurs there is replacement by gray fibrous tissue and bone. Histologically there is, initially, infiltration with eosinophils, lymphocytes, plasma cells, and foreign-body giant cells; there are necrosis and hemorrhages. Later on the infiltrating cells are large and rounded polyhedral foam cells with vacuolated cytoplasm and have comparatively small round nuclei. In the final phases there is connective tissue and bone formation.

The blood picture may sometimes show eosinophils 1.5% to 10%, with mild leucocytosis. Beneficial effects of deep x-ray and cortisone therapy have been reported. Curettage of the lesion is followed by rapid fibrosis.

Because of its histological picture, which resembles that of Hand-Schüller-Christian disease and Letterer-Siwe disease, eosinophilic granuloma is grouped with these entities. These different diseases are considered to represent three different stages in the development of granulomatous reticulosis, a common name given to the group.

The etiology is uncertain. Trauma and virus have been incriminated on indefinite considerations.

Summary

A case of eosinophilic granuloma with exophthalmos in a 7-year-old boy is described. In addition to the skull and the orbit, the scapula was also involved, a lesion probably not reported previously. Curettage of the skull and scapular lesions produced local relief. Exophthalmos was not increased during the period of observation (five months).

Deep x-ray therapy or hormonal treatment could not be tried.

Figures 1 and 2 are by Dr. Maudgal. The skiagrams were taken by Dr. M. M. Paul.

Department of Ophthalmology, Medical College.

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Annual Reviews

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I. Facility of Aqueous Outflow
  A. Measurement
  B. Site and Nature of Resistance
    1. Anatomy
    2. Pathology
  C. Experimental Modification
  D. Clinical Tonography
    1. Diagnosis
    2. Therapy
II. Aqueous Formation
  A. Theory and Measurement
  B. Alterations
    1. Spontaneous and Neurogenic Variations
    2. Carbonic Anhydrase Inhibitors
    3. Other Pharmacologic Agents That Influence Secretion
    4. Surgical Means of Changing Aqueous Flow Rate
III. Episcleral Venous Pressure
IV. Miscellaneous Glaucoma Topics
  A. Visual Fields
  B. Glaucoma Detection
  C. Glaucoma Records and Pamphlets
  D. Nonglaucomatous Aspects of Intraocular Pressure

In recent years important progress has been made in our understanding of glaucoma and the interpretation of intraocular changes in terms of secretion of aqueous, outflow facility, and effects of elevated intraocular pressure on the optic nerve. In addition to providing a convenient simplified scheme for teaching purposes, this mechanical approach has been productive of improved methods of diagnosis and therapy. Although oversimplifying the glaucoma problem, the use of such an outline again for review purposes makes it possible to bring its various sections up to the status of the literature as of July, 1957, and avoids considerable duplication of references and data. The present endeavor is not intended to be complete in itself as to detail or literature of the subjects covered but rather serves as a supplement to the review of last year.[70] This is convenient, for much of the work reported during the past year serves to verify, amplify, and modify prior data as well as resolving some differences of opinion. In addition, basic clinical studies reemphasize earlier conclusions and are leading to the formulation of a more mature view on newer modes of therapy. The use of such an oversimplified scheme, however, is not intended to indicate that a discussion of glaucoma and its complexities must be limited to the pattern outlined. For example, it is apparent that both secretion and outflow may be subject to nervous and vascular controls as well as the possible influences of hormones and metabolic processes occurring elsewhere in the organism. Furthermore, at the present time, many aspects of the regulation of intraocular pressure have not been interpreted in terms of secretion and outflow. Some of the data this year on such alterations of intraocular pressure are discussed arbitrarily under headings that appear most appropriate. Rather than accepting such a mode of action, it is hoped that the reader will consult the original publications and that sufficient doubt will be aroused in his mind to stimulate investigation of the true mechanisms involved.

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I. Facility of Aqueous Outflow

A. Measurement.—The concern echoed in the last year's review about the sources of error in tonography continues to occupy the minds of many investigators. Efforts directed toward avoiding or correcting such errors

are being subjected to further study by workers in this productive field.

1. Standardization of Tonometers: Basic to the clinical determination of outflow facility as well as intraocular pressure is the use of standard tonometers. From the very practical point of view, different laboratories as well as individual ophthalmologists must be speaking of the same procedure with the same instrumentation if data obtained are to have comparable meaning. Therefore, refinements of tonometer testing methods and more rigid specifications are essential.[9,10,301,302,305,352,409,425,524,585,714] The increased interest in testing stations and ingenuity of their mentors are hastening the attainment of these goals. Efforts to improve the design of tonometers are also encouraging.[8,38,844] One of the outstanding achievements along these lines is the improvement of the applanation tonometer so as to eliminate or minimize many of the possible sources of error in this type of measurement as well as to provide a practical instrument for everyday office use.[299,304,571,716]

2. Calibration Tables: The 1955 Friedenwald tables which attempt to correct discrepancies revealed in the 1954 calibration scale for Schiøtz tonometers have been published. These tables and the careful verification of their consistency and validity provide a more adequate basis for tonography values.[267,454] Newer tonography tables calculated from these data and incorporating the average alterations in episcleral venous pressure induced by the tonometer have been in use in several clinics for the past few years.[580] Values obtained for the coefficient of facility of outflow from these tables are some 30% greater than those based on earlier scales. This brings the tonographic estimates of outflow facility into better agreement with those obtained from perfusion studies and flow measurements.[85,261,262] The newer calibration data also serve to reduce greatly or even eliminate some of the discrepancies between tonography values obtained with different plunger weights.[88,300,453,488,495,844,845] Questions have been raised as to the adequacy of the P_t values used for human eyes, especially with heavier tonometer plunger weights.[548] These are being reviewed carefully in several laboratories and may necessitate further revisions. Although the 1955 tables are not to be accepted as the final figures, they certainly appear to be "closer to the truth." They can be recommended for general use by ophthalmologists as the best available from current data.

3. Tonometer Footplate Hole: It has been observed for some time and in several laboratories that tonograms beginning with a scale reading of less than 3 result in falsely increased values for intraocular pressure and, particularly, for outflow facility. In this fashion, eyes with early or borderline chronic simple glaucoma may simulate hypersecretion glaucoma if tonography is carried out with a 5.5 gm. weight. It is therefore a standing rule in many laboratories that sufficient weight must be used in tonography to make the initial reading greater than 3. The mechanism of this puzzling artifact of clinical tonography and tonometry has been elucidated recently in a most convincing fashion. In addition, similar inaccuracies were demonstrated and explained in enucleated rabbit and human eyes.[681] The falsely high values prove to be related to the excessive size of the tonometer footplate hole and the bending of the cornea into the opening created around the plunger at the lower indentation values. At scale readings below 3, this produces a small error in pressure measurements and a considerably larger error in facility determinations. This is a second factor accounting for the higher facility values reported with lower plunger weights. When this artifact is corrected and the 1955 tables are used, differences in facility values with different plunger loads are further reduced.* However, using perfusion methods at much higher pressures, several observers note an increasing resistance to outflow in the enucleated rabbit eye.[263,386,852]

* Becker, B., and Hahn, K.: Unpublished data, 1956.

4. Ocular Blood Volume: A number of studies provide information about the sources of error in tonography related to the unphysiologic conditions induced by the Schiøtz tonometer on the eye.[85,313,314,519,696] As outlined so astutely by Seidel in 1920, the effects of blood pressure, ocular blood volume, and "elasticity of the wall of the globe" must be taken into consideration in addition to aqueous production and outflow.[725] Techniques are available for the determination of variations in ocular blood volume.[104,105,164,272,484,757,871,872] Alterations induced by drugs and various stimuli are being studied. As yet, no precise data are published on the effects of tonography on ocular blood volume.

5. Scleral Rigidity: The assumption in tonography of an average value for the coefficient of scleral rigidity (E) can introduce a very large source of error in outflow facility measurements in those eyes in which E deviates from the mean.[53,88,580,764] This error is magnified because of the misinterpretation of both volume changes and the estimation of intraocular pressure. The availability of the applanation tonometer, with its great advantage of minimal volume changes in the eye not only permits a more precise estimate of intraocular pressure but provides an excellent means of determining the scleral rigidity coefficient for the individual eye.[306,715,844,845] Thus, applanation tonometry followed by Schiøtz tonography with appropriate plunger load affords data on the true intraocular pressure, the scleral rigidity coefficient, and the corrected coefficient of outflow facility. Furthermore, the preceding applanation reading has little or no effect upon the eye and does not appear to alter the subsequent tonographic reading. Caution must be exercised, however, to avoid the introduction of errors related to differences of intraocular pressure in the sitting position used for applanation measurements and the supine position commonly used for tonography.† [304,488,500,761] This is a source of error not only in scleral rigidity measurement but also in attempts at obtaining applanation recovery curves for intraocular pressure after tonography.[844] These discrepancies can be avoided in some patients by the use of a small pillow during tonography or by performing applanation tonometry in the horizontal position.†

Important practical applications of scleral rigidity deviations have been reemphasized in both tonometry and tonography.[306] Appropriate corrections can be made by the use of simplified graphic and algebraic methods.[580] When this information was utilized a number of patients who were suspected of glaucoma by tonometry readings fell into the normal group and 25% of patients thought to have hypersecretion glaucoma on the basis of uncorrected tonograms were found to represent instances of increased scleral rigidity.[59] The latter patients were correctly classified as having normal eyes or chronic simple glaucoma rather than hypersecretion. Of even more importance clinically are those glaucomatous eyes with rigidity coefficients of less than average values. When this occurs in myopic eyes, the diagnosis is further obscured. Changes in vision and visual field resulting from a myopic conus or degeneration and the difficulties in recognizing cupping in such eyes add to the confusion. The finding of normal scale readings on the Schiøtz tonometer provides false assurance of the absence of glaucoma or of its excellent control.‡ [304,414,514] Fortunately, however, even the uncorrected tonographic curves obtained from such eyes are very flat and suggest the diagnosis of glaucoma with hypersecretion. Applanation readings or scleral rigidity measurements reveal the true elevated intraocular pressure. When the coefficient of scleral rigidity is determined for an eye, a corrected calibration scale for the Schiøtz tonometer can be derived for that eye. Thus, a scale reading of 5 with the 5.5 gm. weight may be appreciated as the probable limit of normal pressure for a given

† Moses, R. A.: Unpublished data, 1956.

‡ Goldmann, H.: The Problem of Glaucoma in Myopia, read before the New York Society of Clinical Ophthalmology, Dec. 10, 1956.

myopic eye with decreased scleral rigidity. When this is realized, the patient can then be followed by Schiøtz readings with appropriate interpretation.[304] However, before such a method of following this group of patients can be generally accepted, it will be necessary to demonstrate that the scleral rigidity coefficient remains constant under various conditions and various forms of therapy.[426,519]

Besides the variation of the scleral rigidity coefficient, E, in different eyes, important basic questions have been raised about the validity of the constancy of ocular rigidity for a given eye. Data accumulated in several laboratories suggest that at higher pressure values in individual rabbit eyes this coefficient may increase.[295,624,782] Furthermore, it may be increased in some human eyes by the induced rise in intraocular pressure during tonography.[844] On the other hand, a decrease in scleral rigidity is said to occur with spontaneous diurnal elevations of intraocular pressure in glaucomatous eyes.[519] At present the interpretation of these conflicting reports remains obscure, but they do not appear to be of great clinical significance. Thus, identical average values for scleral rigidity are found before and immediately after tonography.[764] In addition, similar rigidity values are obtained from readings by applanation and with various plunger loads of the Schiøtz tonometer if the 1955 calibration tables are used.[715] However, further scleral rigidity studies on human eyes using the newer calibration tables are awaited anxiously, particularly with reference to spontaneous alterations as well as the effects of intraocular pressure changes, surgery, and various medications.

A method has been devised and applied for the determination of outflow facility which is relatively independent of scleral rigidity measurements.[578] This method is based upon the maintenance of constant intraocular pressure during tonography by the continuous addition of sufficient weight to the tonometer. Thus, the change in volume related to decrease in scleral distention during tonography is eliminated and the volume measurement becomes a determination of the change in corneal indentation. In essence, this method accomplishes perfusion at constant pressure in vivo, substituting corneal indentation for infusion volume. Therefore, when done with several weights, it is theoretically possible to plot volume loss from the eye against pressure during tonography and to derive the facility value from the slope and intraocular pressure from the intercept of the line obtained with the pressure axis. More practically, the method is carried out at one convenient plunger load. When the result is combined with prior applanation readings the influence of scleral rigidity tends to be minimized. Although constant pressure tonography is still not adaptable to routine use, it is comforting to note that the data obtained are in reasonable agreement with values for conventional tonography on the same eyes.[578]

6. Miscellaneous: A number of gadgets have been introduced to improve tonography, including head holders for the tonometer,[559-561] voltage regulators,[35,36] timers,[37] fixation lights,[39] and the correction of nonstandard tonometers.[443] Several of these are of considerable value and under appropriate circumstances improve the validity of the tracings. Attempts to alter the type or site of stress or the degree of pressure applied to the eye are in general disappointing.[112, 113,231,351,366,434,504,517,521,558,589,684-686,749,771] Most of these suffer from the major objection of introducing more unphysiologic conditions and lead to an even greater dependence upon empirical findings. Furthermore, the alleged better separations of glaucoma and normal populations by the various methods suggested are difficult to verify in other laboratories. Perfusion of the anterior chamber in vivo is of considerable interest in verifying the in vitro as well as the tonographic findings, but it is of little practical value in clinical glaucoma.[85,398]

B. The Site and Nature of the Resistance in Normal and Glaucomatous Eyes.—1. Anaotomy: The structure of the normal

trabecular meshwork and angle in several species has been restudied carefully during recent years.[14,34,143,246,672,673,676,797,812] The continued use of tangential sections and various staining procedures permits the appreciation of trabecular structure in greater detail. Efforts to compare the histologic and gonioscopic pictures on the same eye prove most interesting and revealing.[812] The use of the replica method for demonstrating surface anatomy of the angle should provide an important intermediate step in the understanding of this comparison.[840] Although eyebank eyes have been studied in some detail, inadequate data are available on perfusion studies and the histologic picture in the same eye. The extension of such studies to eyes with chronic simple glaucoma and a comparison of the gonioscopic, tonographic, and histologic pictures is under active investigation. The possibility of studying biopsy specimens taken during trephination on glaucomatous eyes offers exciting possibilities for such correlative studies.[812]

Of considerable interest is the demonstration of mucopolysaccharides in the trabecular meshwork.[132,133,839,882] These are visualized in most impressive fashion in animal and human eyes by methyl methacrylate casts of the angle, revealing its surface structure in relief.[837,840] In more conventional fashion the site of the polysaccharides can be visualized when the trabecular meshwork is subjected to a staining method involving the chelation of ferric iron to the acid mucopolysaccharides, followed by a Prussian blue stain for the bound iron.[650] It is even more exciting that the mucopolysaccharides demonstrated can be removed by treatment with hyaluronidase even in paraffin sections of formalin-fixed tissue. This provides histologic evidence for the findings of Bárány on the effects of hyaluronidase on resistance to aqueous outflow. Some areas of confusion still exist, however, since the mucopolysaccharide sensitive to hyaluronidase can be detected in the iris as well as the trabecular meshwork of freshly enucleated human eyes. However, hyaluronidase induces only inconsistent or small decreases in resistance to outflow in perfused human eyes in vitro. This discrepancy may relate to the delay in obtaining the enucleated eyes for perfusion or perhaps to our inability to unravel the multiplicity of events occurring during perfusion.

The histologic demonstration of nerve fibers in the chamber angle of several species raises many questions and much speculation as to their function and role in the control of intraocular pressure.[372,373,838] In addition to these autonomic fibers, the suggestion has been made that a plexus of nerves, ganglion cells, and sensory end-organs in the periphery of the choroid (or pars plana of the ciliary body) may be baroceptors for the regulation of intraocular pressure.[450]

Attempts at exploring the outflow channels in normal eyes by means of labeled isotopes lead to results that can be interpreted in various ways.[591] Thus, if radioactive diiodofluorescein is injected into the anterior chamber of the rabbit or human eye, it is possible to detect radioactivity in the vortex veins. However, rather than accepting these findings as proof of new "invisible" channels of aqueous outflow, one must consider the diffusional exchange of anterior chamber fluid with circulating blood in the iris vessels. Furthermore, in all such injection techniques there is introduced the artifact of the injection itself.[171]

Thus, it appears that, in normal human eyes, major trabecular resistance factors for consideration are the size of the pores, the nature and integrity of the endothelial cells, and perhaps a mucopolysaccharide in the meshwork. In addition, the outflow collector channels and aqueous veins from Schlemm's canal as well as their endothelial linings and scleral surroundings may provide resistance to aqueous outflow.

2. Pathology: In the glaucomatous eye the disordered outflow facility may result from an accentuation of the resistance in the normal eye or additional obstructive factors at other sites. In general, the resistance in

glaucomatous eyes may be divided into pretrabecular, trabecular, and post-trabecular factors or combinations of these. Unfortunately, our lack of knowledge does not permit this classification to be applied clinically except in a limited fashion. The position of the iris and its adhesions, lens alterations, abnormal anterior chamber contents (blood, foreign body, or inflammatory reaction), and congenital defects may all be classified among pretrabecular factors in obstruction to aqueous outflow. Trabecular factors in glaucoma may involve alterations in the size of the pores, the appearance or deposition of abnormal or excessive mucopolysaccharides or other substances, or damage to endothelial cells or to the trabecular fibers themselves. Among post-trabecular factors one must consider obliteration of Schlemm's canal from disease process, degeneration, or congenital defect. Other post-trabecular factors may include obstructions of collector channels and aqueous veins by disease either of the vessels or of their surrounding sclera.[798]

(*a*) Correlation of gonioscopy and tonography. During the past year a number of contributions have appeared on gonioscopy of the chamber angle.§ [185,239,256,362,363,407,450,476,543,567,634,642,705,802, 841] These tend to reemphasize the current clinical classification of glaucoma and to correlate gonioscopic appearance with tonographic findings. Abundant evidence is available that gonioscopy and tonography supplement each other, especially in the diagnosis and treatment of angle-closure and secondary glaucomas. In general, peripheral anterior synechiae and occlusion of the angle tend to correlate with a decrease in facility of outflow. However, large discrepancies can exist in individual eyes. Normal facility values may be found occasionally in the presence of fairly extensive peripheral anterior synechiae. In these eyes the visible damage or adhesions to the anterior chamber side of the trabecular meshwork are apparently not sufficiently extensive to augment the resistance of the normal, apparently uninvolved, major resistance site. Thus no measurable difference in facility of outflow is detected. On the other hand, small alterations at more critical areas may decrease facility markedly even in the absence of extensive visible synechiae. In such eyes the decreased outflow facility may be out of proportion to the visible synechiae. It is possible that variations in the degree of correlation of synechiae and facility of outflow may relate to how deep in the trabecular meshwork the damage occurs following angle closure, flat anterior chamber, hyphema, or other causes of synechiae. For example, evidence is accumulating that hyphema and lens remains may produce more damage to outflow channels than is visible gonioscopically. A disproportionately impaired outflow may also be seen in combined forms of glaucoma such as underlying or superimposed chronic simple glaucoma in the presence of potential angle-closure or secondary glaucoma. In this instance, the site of obstruction may not be visible gonioscopically.

Improved methods for photographing the chamber angle and for the study of the angle in gross embedded histologic specimens provide excellent teaching material for the instruction of ophthalmologists in details of gonioscopy.[215,579,845,846]

(*b*) Angle-closure glaucoma. Gonioscopy is a necessity in the recognition and diagnosis of angle-closure glaucoma.[239] Evidence of closure at the time of pressure elevations is a prerequisite for the diagnosis. The site of resistance is readily appreciated in angle-closure glaucoma. A hypothetical decrease of resistance to deformation of the peripheral iris has been postulated as a causative factor.[417,418,420] If a decreased outflow facility persists in the absence of closure, then one must suspect other damage to outflow channels as a consequence either of bouts of closure or of a superimposed or antecedent chronic simple glaucoma. The familial aspects of narrow angles and shallow an-

§ Scheie, H. G., and Frayer, W. C.: Advantages of Gonioscopy, Exhibit, American Academy of Ophthalmology and Otolaryngology, October, 1956.

terior chambers have been reviewed again and reemphasized as predisposing factors to angle closure.[449,682,803,804] Recently eyes with this type of glaucoma have been found to have a significantly smaller radius of curvature of the cornea than that found in normal eyes of persons of the same age and sex.[805]

(*c*) Chronic simple glaucoma. In chronic simple glaucoma the observation has been made again that the chamber angle reveals no abnormality to gonioscopic examinations but that the backflow of blood into Schlemm's canal is more difficult to induce than in normal eyes.[263,743] Histologic studies on the eyes of a patient with chronic simple glaucoma have demonstrated evidence of degenerative and proliferative changes involving trabecular fibers, Schlemm's canal, and collector channels.[791] The abnormalities are identical with those found to occur in over 10% of eyebank eyes from patients over 40 years of age.[792] However, the specificity of the changes may be questioned in view of their frequent occurrence in otherwise normal eyes.[543] On the other hand, a more detailed study of the tonographic tracings obtained from normal eyes reveals a progressive decrease of average outflow facility with age.‖ [857] This occurs without an increase in intraocular pressure and suggests an associated decline of secretory function. It is for this reason that abnormalities are not detected by tonometry, and the associated hyposecretion also may acount for the lack of damage to the optic nerve. Interestingly, a comparison of perfusion values in the eyes of young (1-2 years) and old (over 8 years) rabbits demonstrates a 30% lower facility of outflow in the older group.[385] Furthermore, the pore size distribution curves for older beef eyes differ from those of the younger animal. With age there is a shift toward more small outflow pores and also a decrease in maximum pore size.[386]

(*d*) Secondary glaucomas. In the secondary glaucomas gonioscopy proves essential for making the diagnosis and also reveals the site or sites of obstruction.[205,353,532] Diagnosis of active peripheral uveitis in some instances can only be made in this fashion.[135] In addition, perfectly white quiet eyes may present the picture of synechiae of preexisting unrecognized uveitis.

Considerable interest has been aroused by recent studies on so-called exfoliation of lens capsule. Several investigators [462,775,776,796] have come to the conclusion that this is rarely a true exfoliation of lens capsule but is rather the deposition of material upon the anterior lens capsule as well as on the ciliary body and in the angle. This accounts for the failure to influence the progression of the glaucoma by lens extraction. The origin and nature of the material deposited remain unknown but should provide an interesting subject for speculation and study. Since it appears to be polysaccharide in nature and not depolymerized by hyaluronidase, it raises the question of the role of an abnormal mucoid in the production of this type of chronic pressure elevation.

Several papers and an excellent symposium on the complications of cataract surgery and their prevention and treatment have been published during the past year.[136, 370,466,542,553,695,758,759,863] Considerable study has been directed toward the relationship of these complications to the tonographic impaired outflow facility and the gonioscopic appearance of anterior synechiae.[476,567] It is clear that even uncomplicated cataract extraction can result in some damage to outflow channels. Operative and postoperative complications increase the incidence of synechiae and of impaired outflow facility to unexpectedly high levels. Only when extensive enough do these result in secondary glaucoma. Most prominent among the complications that contribute to obstructed outflow are rupture of the lens capsule and loss of vitreous at the time of surgery and the occurrence of shallow or flat anterior chambers postoperatively.

An interesting report has appeared on three eyes with rubeosis iridis with spontaneous improvement.[259] Furthermore, the disappearance of the new-formed vessels

‖ Becker, B.: Unpublished data, 1956.

was associated with improvement in outflow facility to normal values. This may also be accomplished occasionally by cycloanemization and by x-irradiation.¶ [652] These findings should encourage ophthalmologists to believe that hemorrhagic glaucoma is not always a hopeless situation and that in the earlier stages of the disease a normal trabecular meshwork and Schlemm's canal system can exist beyond the neovascularized obstruction. However, most eyes enucleated for hemorrhagic glaucoma demonstrate extensive damage to outflow channels. Anticoagulants are reported to improve the prognosis following vein occlusion, especially if employed in "imminent" occlusion.[438] On the other hand, in the experience of other observers such therapy fails to be of benefit in preventing the secondary glaucoma.[388]

In the hemorrhagic glaucomas that follow vein occlusion, a high index of suspicion of preexisting glaucoma should be maintained.[438,488,701,741,742] In a series of 18 consecutive patients with unilateral hemorrhagic glaucoma referred to one tonography laboratory, 14 (78%) had evidence of chronic simple glaucoma in the opposite eye.[78] The recognition of this relationship is of even greater significance since the patients involved are often essentially one-eyed. Not only is the opportunity afforded for the early diagnosis and control of the contralateral glaucoma, but also the possibility is presented by so doing of decreasing the risk of vein occlusion in this eye.

Heterochromia iridis with elevated intraocular pressure in the eye with increased pigmentation should always suggest a diffuse malignant melanoma of the iris.[679] However, the glaucoma that appears with some choroidal tumors still remains an unsolved problem.[379,523,547] It is of further interest that a number of eyes with malignant melanomas of the choroid present decreases in outflow facility without elevations of intraocular pressure.# In fact, some of these eyes have marked hypotony.

¶ Becker, B.: Unpublished data, 1955.

Becker, B.: Unpublished data, 1956.

Further observations have been reported on endothelial dystrophy and glaucoma,[607] on iris atrophy and glaucoma,[149,432,824,867] on the importance of gonioscopy in the recognition of foreign bodies in the angle,[177] on nevoxanthoendothelioma and its associated unilateral hemorrhagic glaucoma in young infants,* [541,593] on glaucomatocyclitic crisis and its differential diagnosis,[146,184,638,689] on phacogenic glaucoma,[247,287,357,380,883] on traumatic glaucoma,[31,153,481,491] and on the effects of irradiation on outflow facility.[397]

(*e*) Congenital glaucoma. A number of cases of congenital glaucoma have been reported and reviewed with discussion of its familial aspects, its frequent occurrence in the Sturge-Weber syndrome, and its occasional association with retrolental fibroplasia and hypoparathyroidism.[178,201,290,350, 501,556,617,637, 657,667,767]

It is of considerable interest that the cleavage defect characterizing congenital glaucoma may occur without enlargement of the globe and manifest itself later in life as juvenile glaucoma or even as adult chronic simple glaucoma.[439,469,859] When appearing in these delayed forms it may be hereditary or it may be associated with the Sturge-Weber syndrome or with other congenital defects of the eye.[144,458,531,687,767] The question has even been raised as to whether all chronic simple glaucoma has as its basis congenital or developmental anomalies.[748] Support for this point of view may be marshalled from the fact that there is not only a higher incidence of glaucoma in the families of patients with chronic simple glaucoma, but an even greater number of relatives with decreased facility of outflow in the absence of pressure elevation.† [109,853] In fact, evidence is available that some eyes with secondary glaucoma (traumatic, aphakic, etc.) may have an antecedent underlying outflow impairment.[333,491,567] Some patients with secondary glaucoma develop chronic simple glaucoma in the opposite un-

* Sanders, T. E.: Personal communication to the author.

† Becker, B.: Unpublished data, 1956.

injured or unoperated-on eye at a later time. That glaucoma may have a congenital or developmental anomaly as its basis is true in a sense for angle-closure glaucoma. Here one does have a familial history of narrow angles as well as a congenital, structural anomaly as a basis for the glaucomatous process.

At the other extreme is the suggestion that all glaucoma is secondary to trauma or inflammatory disease. This seems hardly likely and is denied by other investigators.[491,677] The most likely thesis at present is that chronic simple glaucoma has as its pathologic basis degenerative and proliferative changes in the trabecular meshwork and Schlemm's canal system. Data are badly needed as to whether eyes with early chronic simple glaucoma present these changes to a degree not found in normal eyes. It would also be of interest to learn if families that are predisposed to glaucoma have a greater number of such proliferative changes to correlate with the increased incidence they present of tonographic outflow facility changes. Perfusion studies and histologic examinations to date on glaucomatous eyes have been accomplished largely in advanced cases.[260,315] In these, secondary changes may obscure the initial pathology. This serves to reemphasize the need for correlated studies on eyes with early chronic simple glaucoma.

Questions arise as to whether there are reversible stages of obstruction to outflow with or without organic changes. Occasionally untreated glaucomatous eyes demonstrate considerable variation in outflow facility. Certainly reflex decreases in outflow facility are observed in normal eyes and are reversible. The relation of such alterations to glaucoma remains undetermined. This subject is being actively explored in a number of laboratories.

C. The Experimental Modification of Resistance to Aqueous Outflow.—1. Obstruction to Aqueous Outflow: Efforts to obstruct aqueous outflow experimentally continue to occupy investigators in several laboratories.‡[384,626] It is possible to raise intraocular pressure and obstruct outflow by intraocular pressure and obstruct outflow by the injection of various foreign substances into the anterior chamber. It is also possible to accomplish this by cautery of aqueous veins. In most instances these procedures produce a temporary rise in intraocular pressure and are followed by hypotony and a marked decrease in the rate of secretion of aqueous. A similar temporary rise in intraocular pressure can be induced by tying off the vortex veins. Interestingly enough, aqueous outflow facility as measured by tonography remains normal in such eyes even during the hypertensive phase of vascular engorgement. This is important evidence confirming the minor role of vortex veins in the outflow of aqueous humor, as well as the lack of significant effect of elevated intraocular pressure on tonographic measurements of the outflow facility coefficient.

Attempts at altering the outflow facility by perfusion with particles of controlled size in rabbit eyes suggest that latex particles of diameter 0.138μ to 1.71μ all tend to induce similar reductions in outflow facility.[626] Thus, the perfusion estimate for outflow facility of 0.20 is reduced to 0.08 following the latex infusion. The decreased facility induced by the particle injections is no longer altered by hyaluronidase. This study needs amplification along several lines. It is curious that the same outflow facility was obtained with particles of more than tenfold variation in diameter. The question arises as to the effects of particles of much smaller size. It would also be of interest to know whether latex particles of much larger size would reduce the facility of outflow to zero. Among the difficulties with the use of latex particles in high concentration, however, are the effects of viscosity of the perfused fluid on the measured outflow facility.

Other observers note no obstruction with other particles varying from 0.1μ to 0.5μ, but these experiments need repetition with

‡ Oglesby, R. B.; Gay, A. J., and Becker, B.: Unpublished data, 1956.

estimates of outflow facility.[384] A rise in intraocular pressure follows the intracameral injection of dead Serratia marcescens (Bacillus prodigiosus) (0.75μ), and more complete block of outflow channels by Angiopac (1.5μ) is reported to occur in rabbits.

When red blood cells are used in attempts to obstruct aqueous outflow and to simulate the condition of traumatic hyphema in experimental animals, elevations of intraocular pressure are rarely induced.[23,583] Although hemolyzed red cells leave the anterior chamber much more rapidly, it is of considerable interest that red blood cells can apparently pass out of the rabbit anterior chamber intact. This is evidenced by experiments employing labeled red cells.[735] However, there is a large source of error introduced in these experiments by the necessity for injecting blood cells into the anterior chamber. This may alter the permeability of vessels surrounding the chamber. In this regard systemic or subconjunctival trypsin fails to hasten the absorption of experimental hyphema in guinea pigs unless given in large enough doses to induce severe ocular and systemic reactions.[415] Streptokinase and streptodornase also prove ineffective in the resorption of intraocular hemorrhages in rabbits.[522]

Other agents used to increase intraocular pressure and obstruct aqueous outflow in the rabbit are the introduction into the anterior chamber of sodium bicarbonate,[424] the compression of neck veins, the application of atropine,[431] and the systemic administration of sanguinarine or related compounds.[473] Sanguinarine is also reported to damage the trabecular meshwork of monkeys and to induce a rise in intraocular pressure. More recently experiments suggest that systemic citral administration obstructs the outflow channels of the rabbit and monkey eye, and that this effect is reversed by cystein, dimercaprol (Bal), or vitamin A.§ [474] One of the suggestions deduced from these preliminary studies is that vitamin A deficiency may play a role in the alterations of outflow facility that characterize the glaucomatous state.[474,648] This interesting speculation needs amplication and verification.

2. Hyaluronidase: The use of hyaluronidase from various sources (testicular, staphylococcal, and snake and bee venoms) demonstrates almost identical drops in resistance of the perfused chamber angle of cattle eyes.[59] It thus seems clear that there is a mucopolysaccharide in certain animals eyes that contributes to the resistance to aqueous outflow.[263,621] In the eye of the tawny owl the corneal endothelium is covered by a thick layer of a hyaluronidase-sensitive mucoid.[61] The origins of this mucoid and the one or more in the trabecular meshwork remain matters of speculation. Local synthesis by endothelial cells is a good possibility. Another likely source is by trabecular filtration of vitreous hyaluronic acid or its breakdown products carried forward by the aqueous humor.[58,103]

The mucopolysaccharides can be hyaluronic acid, one of the chondroitin sulfates that are sensitive to hyaluronidase, or any other polysaccharide hydrolyzed by this enzyme. Further details of its intimate nature may be revealed by the use of recently isolated more specific depolymerizing enzymes or by microchemical analysis.[381] Of considerable interest is the finding reviewed above that in human eyes there is also a polysaccharide sensitive to hyaluronidase,[133, 882] but in this species the administration of hyaluronidase does not appear to produce significant or consistent alterations in outflow facility.[85,261,621] The introduction of hyaluronidase into the anterior chamber of living rabbits does not appear to produce alterations of outflow facility of an amount and degree that can be measured by tonographic methods.‖ This may stem from the difficulties and artifacts of tonographic measurement on a recently injected eye. Fur-

§ Lloyd, J. P. F.: Citral Poisoning, read before a meeting of the Nutritional Society, May, 1956.

‖ Becker, B. and Constant, M. A.: Unpublished data, 1956.

thermore, as noted above, following anterior chamber hyaluronidase injection in the living rabbit there is a rapid return to normal perfusion values as measured in the enucleated eye. The restoration of resistance to outflow under these circumstances occurs in such fashion that sensitivity to alteration by hyaluronidase is lost in part.[60] On the other hand, the subconjunctival injection of hyaluronidase is said to lower intraocular pressure in rabbit eyes.[783] This finding in rabbits resembles the previously reported ocular hypotension induced by similar subconjunctival injections in patients.¶

Abnormalities in hyaluronic acid-hyaluronidase balance within the eye are described speculatively as playing possible roles in the pathogenesis of glaucoma.[448,562] Furthermore, the possible relationship of an altered hyaluronic acid to glaucoma and other disease processes of the eye may receive some support from recent preliminary reports on structural changes in the rabbit eye produced by a sulfated derivative of hyaluronic acid.[342] Finally, since there are reversible variations in outflow facility with volume of anterior chamber, it is apparent that alterations in vitreous structure or volume may affect outflow facility.[84,257,261] The clinical significance of such anterior chamber and vitreous volume alterations remains obscure.[747] It is clear that there is still much to be learned about the nature of the vitreous body and the site of formation of its hyaluronic acid as well as the possible role of polysaccharides in the secretion and outflow of aqueous humor.[51,66,168,354,355,719-721,754,882]

3. Neurogenic and Related Alterations: Considerable interest has been aroused in the neurogenic control of aqueous outflow. The innervation of the ciliary muscle by sympathetic and parasympathetic fibers and the demonstration of nerve fibers in the chamber angle of many species have led to a number of interesting investigations.[372, 554,672] More recently, vital staining with methylene blue, silver impregnation techniques, and nerve degeneration studies reveal that autonomic fibers, especially parasympathetic ones, innervate the chamber angle.[373] The question of the presence of afferent fibers in the chamber angle remains unanswered, and specialized receptors are not visualized. On the other hand, baroceptors are described in the extreme periphery of the choroid.[459]

Compensatory decreases in facility of aqueous outflow follow various methods of decreasing the rate of secretion of aqueous, in both human and animal eyes.[69,174,640] Furthermore, a temporary compensatory increase in the hyaluronidase-insensitive resistance to outflow is reported to occur in rabbit eyes after the in vivo anterior chamber injection of hyaluronidase. The reflex nature of this decrease in outflow facility is suggested by its partial inhibition by ganglionic blocking agents.[60] Interesting consensual alterations in outflow facility are noted sporadically in rabbit eyes, such as those following experimental obstruction of outflow in the contralateral eye.[384]

The stimulation of sympathetic and parasympathetic nerves in cat and rabbit eyes can produce alterations in aqueous outflow facility even in the enucleated eye.[644] This is of considerable interest when taken in conjunction with the effects of various autonomic drugs on aqueous humor dynamics.[68,400,431,602] Associated with the improved tonographic outflow facility that follows pilocarpine administration to monkey eyes, impressive alterations in the trabecular meshwork are demonstrated.[248,249,676] These studies result in the reasonable conclusion that the openings in the trabecular meshwork are enlarged by pilocarpine administration. The insertion of elastic tendons of the ciliary muscle into the trabecular meshwork and scleral spur offers possible mechanisms for these changes.[672,726] Furthermore, in normal human eyes there is evidence that accommodation is associated with an increase in out-

¶ Moor, W. A., and Shahan, P. T.: Spreading Factors in Ophthalmology, read before the Midwest Section of the Association for Research in Ophthalmology, St. Louis, Nov. 17, 1947.

flow facility as compared with the same eyes after relaxation.[29]

On the other hand, the administration of mydriatics does not appear to alter tonographic outflow facility in normal human eyes. However, in cats and rabbits dilatation of the pupil is said to increase the resistance to aqueous outflow from the anterior chamber.[727] In eyes with known chronic simple glaucoma mydriatics may counteract the effects of miotic therapy, thus decreasing outflow facility. More data are needed relative to the effects of mydriatics on the impaired outflow of eyes with untreated chronic simple glaucoma.

D. Clinical Tonography.—Reports continue to appear on the value of tonography when used in association with conventional methods of examination in the diagnosis and evaluation of therapy of various types of glaucoma.[195,254,284,327,361,394,488,490,540,552,608,668,699,707,847,848] Questions arise as to whether this procedure should be limited to research laboratories and glaucoma centers or whether tonography should became a routine office procedure.[311,316] Both of these alternatives are proving successful, and there are obviously advantages and disadvantages to each. However, successful application of tonography demands a large volume of clinical material and the time and efforts of an ophthalmologist interested in glaucoma. Furthermore, tonography must be done with carefully calibrated equipment and by experienced personnel. In addition to the sources of error inherent in the method and the assumptions made (see above), there are a number of potential errors that stem from the faulty techniques of beginners. It is a common experience that the first 500 or 600 tonograms done by a technician cannot be relied upon to provide useful information. Such tracings may demonstrate lack of transmission of cardiac pulse because of the sticking of a dirty plunger or poor position of the tonometer on the eye. Inadequate explanation or noisy surroundings may fail to provide adequate cooperation of the patient. Inadvertant pressure on the globe, stimuli to rapid blood pressure alterations, and a high incidence of initial irregularities in the tonogram (especially a rapid fall in the beginning of the tracing) are also common sources of errors which may make the interpretation of these tonograms difficult. As with any laboratory procedure, conclusions should not be drawn hastily from single tracings, especially the initial tonographic experience of a patient. It is clear that tonography cannot replace careful ophthalmologic examination and the judgment of experience. However, the data obtained from repeated consistent tonograms provide useful additions to our knowledge about the status of the individual eye.

1. Tonography and Glaucoma Diagnosis: (*a*) Congenital glaucoma. In congenital glaucoma there is now additional evidence that the facility of outflow is decreased.# [25,617] Tonography assists in the differential diagnosis of congenital glaucoma and megalocornea and is particularly helpful in those eyes with borderline values for intraocular pressure. Tonography under general anesthesia may introduce errors, however. Variation in depth of anesthesia as well as alterations in the rate of secretion induced by the anesthetic agent may make interpretation hazardous.

(*b*) Angle-closure glaucoma. In the diagnosis of angle-closure glaucoma, the application of the darkroom test or pupillary dilatation by means of mydriatics proves of considerably greater value when combined with tonography.[77,251] Thus, although these procedures can induce pressure rises in eyes predisposed to angle-closure,[142,252,328,568] in many instances a decreased outflow facility occurs in such eyes without significant pressure elevation. In a large series of eyes subjected to a darkroom test [251] and a similar independent series subjected to mydriasis,[77] a decrease of 25% to 30% in facility of outflow was found to be the best criterion for separation of the findings in eyes with angle-closure glaucoma and normal eyes. With these procedures and the arbitrary

Becker, B.: Unpublished data, 1956.

change chosen as significant, it becomes possible to recognize angle-closure glaucoma in 85% to 95% of cases in comparison with the 45% to 50% response to the usual provocative tests.[252,486] These improved methods of detection are obviously of considerable importance in a disease process in which prophylactic surgery is curative.

Caution must be exercised in carrying out mydriatic tests on eyes suspected of angle closure. It is probably best to perform the darkroom test first. If it proves negative, then Euphthalmine, homatropine, or Cyclogyl can be applied to one eye only and should be followed by miotic therapy until the pupil is constricted. The dangers of the instillation of mydriatics in these eyes [285] and even of the systemic administration of antispasmodic drugs have been demonstrated repeatedly. These were emphasized again in an excellent scientific exhibit at the 1957 American Medical Association Meeting.*

(*c*) Chronic simple glaucoma. In the early detection of chronic simple glaucoma the finding of a flat tonographic tracing or the induction of such a tracing by a water provocative test is proving of increased importance.[81,92,358,539,843] It is of interest that even eyes with low scleral rigidity, such as those of the group described above with glaucoma associated with myopia, demonstrate falsely low tension readings † [304] but remarkably flat tonographic tracings.[751] Suitable corrections for the low scleral rigidity reveal tensions considerably more elevated and facility of outflow less decreased than was originally suspected. However, the flat tonographic tracings obtained from these eyes and the elevated P_0/C values suggest the possible diagnosis of glaucoma even before the scleral rigidity correction is applied. The use of a ratio P_0/C [77,92,488] greater than 100 continues to prove of value in the recognition and early diagnosis of glaucoma, particularly when evaluated after the drinking of a liter of water. It also appears to be a valuable rapid method of evaluation of the status of control of glaucoma by a given type of therapy. An excellent review of diagnostic and provocative tests has been presented,[328] and a most interesting discussion on the diagnosis and therapy of glaucoma has been published.[488]

2. Tonography and the Therapy of Glaucoma: (*a*) Medical treatment. Several reviews are available on miotic therapy, its mode of action, complications, and prognosis.‡ [2, 19, 150, 189, 332, 421, 444, 565, 582, 611, 643, 683, 769, 779, 856]

It is generally agreed that pilocarpine and eserine [857] improve outflow facility in chronic simple glaucoma. The water provocative test in patients with treated glaucomatous eyes fails to indicate the adequacy of control of intraocular pressure in glaucoma but may predict future pressure rises in eyes with apparently normalized tensions.[491] Although the degree of control does correlate with the improved outflow facility coefficient, the variation in the vulnerability of the individual optic nerve to a given pressure makes the tonographic findings only suggestive, reassuring, or warning signals, as the case may be. The ultimate status of control must be defined in terms of progression of ocular damage.

Newer miotics have been introduced and evaluated. One of the most interesting of these agents is echothiophate (Phospholine) iodide.[480] The miosis induced by this drug lasts as long as that following isoflurophate (Floropryl), but echothiophate iodide is water-soluble and stable, with few side-effects (brow ache, nausea, myopia). In 0.25% solution it proves effective in lower-

* Cholst, M.; Goodstein, S.; Berens, C., and Cinotti, A.: Glaucoma in Medical Practice: Danger of Systemic Antispasmodic Drugs in Predisposed and in Diagnosed Glaucomatous Eyes, Scientific Exhibit, American Medical Association Meeting, New York, June 3-7, 1957.

† Goldmann, H.: The Problem of Glaucoma in Myopia, read before the meeting of the New York Society of Clinical Ophthalmology, Dec. 10, 1956.

‡ Leopold, I. H.: Recent Advances in Medical Therapy of Glaucoma (10th Schoenberg Memorial Lecture), presented at a meeting of the New York Society of Clinical Ophthalmology, Dec. 10, 1956.

ing intraocular pressure even in some eyes uncontrolled on other miotics. The very potent anticholinesterase miotic, decamethylene-bis-N-methyl carbaminoyl-*m*-trimethyl ammonium phenol (BC48), has received additional testing.[289,480] It is stable and water-soluble. In 1% solution it can overcome 1% atropine and produce miosis that lasts longer than that resulting from isoflurophate. Reports are enthusiastic as to the efficacy of this compound in the therapy of glaucoma, as well as its remarkable duration of action and its freedom from side-effects. Both echothiophate iodide and BC48 are recommended for chronic simple and aphakic glaucoma but not for the angle-closure group.

The miotic Mintacol (diethyl *p*-nitrophenyl phosphate) is also water-soluble, long-acting, and capable of overcoming the pupillary effects of atropine. It has received more extensive study in glaucoma therapy, and reports continue to be enthusiastic as to its efficacy.[611] The Russian miotic tetraethylmonothiopyrophosphate (A_2) appears to have much the same characteristics and actions as its analogue tetraethylpyrophosphate (TEPP).[815] It is not water-soluble or stable but proves to be an effective miotic agent for the treatment of glaucoma.

The use of combinations of miotics remains somewhat controversial but is recommended by a number of ophthalmologists.[173,382,492] A report of a potentiating effect of Mintacol and prostigmine on the inhibition of iris cholinesterase lends support to the use of this mixture.[493] Problems of sterility, stability, and absorption of miotic preparations continue to receive consideration.[243,298,663]

One of the basic unanswered questions about chronic simple glaucoma concerns the effects of miotic therapy on the progression of the outflow defect. It is hoped that this can be answered by repeated tonographic tracings extended over a long period of time. It is difficult, however, to obtain adequate controls for such studies, and few data are available on the life history of glaucoma in terms of its outflow disorder. Miotic therapy improves outflow facility, but it is not known whether this is merely a bypass of the obstruction, a reversal of that part of the alteration that is capable of improvement, or a true modification of the disordered pathology itself.[779] Although vision and visual fields can be preserved by adequate control of intraocular pressure, the question of preventing progression of the obstruction by miotics requires answering before one can decide whether to treat with maximum frequency and concentration of miotics or with the minimum needed to lower intraocular pressure. This information is also essential for making reasonable statements as to the prognosis of glaucoma subjected to medical therapy.[297,545]

(*b*) Surgical treatment. In the surgical therapy of glaucoma there appears to be increasing evidence and favor for early surgery in angle-closure and congenital varieties and for the conservative handling of chronic simple glaucoma.[30,126,330,369,405,544,704,706,772,778]

In congenital glaucoma goniotomy and various modifications of this procedure continue to be recommended.[63,129,145,244,350,544] There are indications from tonography that successful goniotomy does improve outflow facility, even after recovery from the stage of hypotony.[25]

In angle-closure glaucoma, tonography provides useful complementary data to those provided by gonioscopy in the decision as to whether to perform an iridectomy or a filtering operation.[842] It is not always possible preoperatively to distinguish iridocorneal contact from anterior synechiae by gonioscopy.[253] Gonioscopy in the operating room after deepening the anterior chamber with saline may help to differentiate the true synechiae.§ Ultimately however, it is the functional capacity of the trabecular system that determines the success of iridectomy. If evidence can be obtained that the outflow facility is adequate under medi-

§ Shaffer, R. N.: Presented at a meeting of the American Ophthalmological Society, May 30, 1957.

cal therapy, peripheral iridectomy has been demonstrated to prevent acute attacks and cure the angle-closure aspects of the disease. After the iridectomy it is then possible and necessary to evaluate trabecular function and determine whether or not medical therapy is indicated. By this means it is possible to control a number of patients with acute or chronic angle-closure glaucoma by iridectomy alone or with medication, in spite of rather extensive peripheral anterior synechiae, repeated attacks, or a long interval in a given attack.‖ With use of the 1955 Friedenwald tables as a basis for calculating tonography, an outflow facility of 0.10 or greater preoperatively usually proves adequate for medical control after peripheral iridectomy. The suggestion of an iridectomy in the fellow eye in patients with angle-closure glaucoma is a routine recommendation in an increasing number of glaucoma clinics and ophthalmologists' offices. It is apparent that over 50% of such fellow eyes will develop glaucoma even under the best of medical therapy.[4,49,350,531,568] In these eyes, which usually present very adequate outflow facilities, peripheral iridectomy is almost invariably preventative and "its prognosis is statistically better than that of crossing a London street." [219] Alterations in number, form, and methods of carrying out the iridectomy are described.[121,196,356,437]

The iridencleisis operation continues to have ardent advocates [95,140,230,359,467,600,609,629,697,737,766,818,819,832,833] and is suggested by some authors for use in congenital glaucoma [439,468] as well as for some eyes with angle-closure and chronic simple glaucoma. In a series of patients with angle-closure glaucoma subjected to iridencleisis it is of interest that outflow facility and pressure could be normalized in approximately 80% of eyes.¶ Of particular importance is the fact that the prognosis for normalizing both of these functions by this procedure in angle-closure glaucoma appears to be equally good in those eyes with markedly impaired outflow facility, those that failed to be normalized by iridectomy, and those with excellent outflow facility preoperatively. This is an important observation, which indicates that any eye with angle-closure glaucoma that has adequate outflow facility or even borderline facility can be subjected to peripheral iridectomy. If iridencleisis then proves necessary, the prognosis for this operation is as good as if it had been done as a primary procedure. It further suggests that there is no excuse for performing an iridencleisis, with its complications and frequent compromise of normal outflow channels, as initial surgery on an eye with an adequate facility of outflow.

The dreaded occurrence of malignant glaucoma following surgery on eyes with angle-closure has stimulated a number of reports.[107,108,179,506,688] Since this disease process proves so difficult to treat, the suggestion is made that the prodromata of a relatively large lens and narrow angles be recognized. The prophylactic extraction of the lens combined with a filtering procedure is then advocated.[108] However, this rare condition is difficult to distinguish before it occurs from the common more easily treated angle-closure glaucoma. Although most observers agree that prompt lens extraction is advisable in malignant glaucoma, there are few instances where one can be certain enough of the prodromata to carry out this operation initially on a first eye.

The prime consideration in the surgery of chronic simple glaucoma continues to be evidence of progressive loss of visual field in spite of efforts at medical therapy.[359,545,704,706,753,772] It is important to reemphasize that tonography, when performed carefully and suitably corrected for the individual eye, provides valuable information about the progress and control of glaucoma.[213] This laboratory test can supplement and corroborate other findings but is not a substitute for good clinical judgment in the handling of the individual patient.

‖ Becker, B., and Thompson, H. E.: Unpublished data, 1956.

¶ Becker, B., and Thompson, H. E.: Unpublished data, 1956.

A number of reports have appeared on standard surgical procedures, their results, complications, and modifications, as well as on combinations of various filtering operations.# [18,62,98,172,196,211,240,245,286,375,387,403,416,435,538,551,555,590,647,655,659,693,723,752,778,780,781,786,787,794,826,829,860,864,884] Data on the effects of these and other surgical approaches on scleral rigidity are needed in order to learn more about their modes of action and to obtain a real picture of their ability to control intraocular pressure. Progressive field loss in spite of normalized Schiøtz readings may mean a decreased rigidity masking the pressure elevation.

II. Aqueous Formation

A. Theory and Measurement.—As indicated in last years' review, the two major methods available for estimation of the rate of secretion of aqueous humor are tonography and the turnover of systemically administered test substances. Tonography, its sources of error and correction factors, are reviewed in the preceding section. The general theory for the turnover of test substances in the aqueous humor has been reviewed, amplified, and subjected to critical appraisal in a superb presentation at the Second Conference on Glaucoma sponsored by the Macy Foundation.[422] Here one of the men most responsible for the development of this theory had the opportunity to present it for informal discussion to a group of clinicians and basic scientists with a common interest in processes of active transport and secretion. With suitable modifications the general mathematical formulations discussed in last years' review have been found to fit the data available.[71,208,423] The elaboration of events in the vitreous, lens, and cornea have been amplified,[40,546] but the essential validity of the theory has not been disputed seriously.[419,612,613]

Recent studies confirm details of the histology of the ciliary body of animal and human eyes[674,675,724] as well as the postulated roles and significance of "secretory vacuoles" and mitochondria. In addition, a study of sections of the rabbit ciliary epithelium as viewed with electron microscopic magnifications[376] is presented in an interesting monograph. Although the interpretation of such data are matters of controversy, excellent photographs are presented to demonstrate the "cytomembranes," vacuoles, cell membranes, basement membranes, nucleus, and Golgi apparatus of the ciliary epithelial cell. Of particular interest in this secretory cell are the relatively small mitochondria and the cytoplasmic vesicles.

A number of secretory processes are influenced by the rate of oxidative phosphorylation. Furthermore, oxidative phosphorylation can be coupled to active transport in the isolated mitochondria of a number of cells. It is suggested that these particles may play the role of pumps which enable the cell to do osmotic work.[639] Further studies are reported on the presence and intricacies of oxidative phosphorylation in ciliary processes and its role in the secretion of aqueous humor.[55] Much of the oxygen uptake by ciliary homogenates appears to be related to the synthesis of adenosine triphosphate. The basic cyanine and styrylquinoline dyes which interfere with formation of aqueous humor probably do so by uncoupling oxidation from phosphorylation.

The intimate mechanism by which the transport of aqueous humor into the eye takes place remains speculative. The original Friedenwald "redox pump" hypothesis of an active transport of electrons resulting in the formation of hydroxyl ions in the epithelium and their transfer to the posterior chamber predicts the posterior chamber chemistries as found in the rabbit and guinea pig.[79,423] In these species there is a higher pH, an excess concentration of bicarbonate, and deficit of chloride in the aqueous humor as compared with plasma values.

Scheie, H. G.: Cataract Extraction Following Filtering Operation for Glaucoma (a motion picture), 61st Annual Session of the American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 16, 1956.

humor [72,654] confirm the older findings [33,364] However, recent analyses of human aqueous of an excess of chloride in the anterior chamber as compared with arterial plasma. Furthermore, human aqueous humor has a lower pH and bicarbonate concentration than does plasma.[72,192,193] Thus, the data for human eyes resembles those reported for the monkey.[192]

As might be anticipated, the posterior chamber aqueous of primates also demonstrates greater deviations from plasma values than does the anterior chamber concentration. Thus, in a normal human eye at a plasma chloride concentration of 114 mM. per kilogram of water, the anterior chamber contains 121 mM. per kilogram of water and the posterior chamber aqueous chloride concentration was 134 mM. per kilogram of water. In a normal monkey corresponding values for chloride concentration in milimoles per kilogram of water were plasma, 116; anterior chamber, 128, and posterior chamber, 135.* These findings suggest that, if the Friedenwald hypothesis is to hold true, the transport of electrons may take place in the opposite direction in primate eyes than in rodents, with the production of hydrogen ions which are secreted into the posterior chamber. This would resemble the "redox pump" mechanism as it has been applied to the gastric mucosa.[175] In the posterior chamber an exchange of the cation sodium for hydrogen might take place, much as postulated for the renal tubule.

However, the Friedenwald hypothesis in its original form meets with other difficulties in explaining the secretion of aqueous humor even in the rabbit eye. In the ciliary body, as in the frog skin and other secretory cells, there appears to be inadequate oxygen consumption for this type of transport.[54, 101,471,616] Suggestions that sodium is the ion actively transported are attractive [54,194,422] but need further experimental data for confirmation and leave open the question of the intimate details of the process.

* Becker, B., and Constant, M. A.: Unpublished data, 1956.

The question of the mechanisms of active transport is not unique to the aqueous humor. It is a problem that is a subject of current debate and speculation as well as experimental work in many fields. Current literature abounds with papers on active transport and secretion by various exocrine glands as well as the renal tubule, frog skin, red cell, stomach, choroid plexus, and the individual cells.[67,170,175,176,191,222,226,371,402, 410,471,472,515,618,628,653,744,745, 795,814] In spite of much progress and considerably more information about the conditions, measurements, and alterations of the transport process, similar problems as to energetics and as to the nature of the ion or ions transported remain largely unresolved in each of these specialized areas.

With regard to the aqueous humor, in spite of incomplete knowledge at the present time, concentrations of substances in the posterior and anterior chambers and, in particular, the turnover of substances in both chambers provide data for estimating the rate of aqueous flow as well as the diffusional exchange of the substances. These calculations are essentially independent of the intimate mechanism by which the aqueous humor or the substances in question enter and leave the eye.[71,75,423] Interesting problems arise in interpreting the turnover data in the posterior and anterior chambers for systematically administered bicarbonate.[323,324] The small deviations from anticipated average values may stem from experimental errors or may be related to a more rapid diffusional exchange than anticipated for this ion in the anterior chamber because of its equilibrium with highly diffusible carbon diozide. Similar explanations may be offered for the discrepancies found in these experiments between the altered K_P:K_D ratios for steady-state bicarbonate concentrations in the absence of tonographic changes.[422] On the other hand, alterations in the diffusion coefficient, K_D, for bicarbonate may result from the alkaline infusion.

The study of anterior chamber concentrations alone or comparisons of anterior cham-

ber and plasma values provide interesting leads for more detailed study and have furnished the subject matter for endless speculation. Unfortunately, without knowledge of precise simultaneously obtained posterior chamber concentrations, it is not possible to interpret the significance of these findings in terms of secretion and diffusion. Thus, a large volume of work that has been reported and reviewed in recent years needs repetition with appropriate posterior chamber analyses.

Posterior chamber data cannot be obtained readily in human eyes, and we must content ourselves with educated guesses based on adequate animal experiments. Nevertheless entertaining speculation is aroused by the findings that the chloride content of the human aqueous humor is not influenced by the presence or absence of cataracts,[654] that it is lowered relative to plasma concentrations by the administration of acetazolamide, and that the chloride excess in the anterior chamber correlates well with the tonographic estimate of the rate of aqueous secretion.[72] Of related interest are reports that cataractous eyes have the same ascorbate and hydrogen ion concentrations in the aqueous humor as do normal eyes.[165,630]

Sodium and potassium concentrations in the aqueous humor have been the subjects of further studies.[122,192,233,255,343,483,664,666] Most observers are in agreement that in the rabbit eye there is a small (about 2% to 3%) excess of sodium in the anterior chamber as compared with a dialysate of plasma. Potassium is found to be in slight deficit in the anterior chamber by some observers,[483] but others note a small excess in the rabbit eye.[343] Because of the very small discrepancies from plasma values and the errors involved in flame photometry, efforts to modify concentrations of these ions relative to plasma present considerable technical difficulties. Furthermore, most of the current data on the effects of the administration of acetazolamide or other agents are limited to the anterior chamber concentrations of these cations and therefore are even more difficult to interpret.

As indicated in last years' review, one of the simpler methods of measurement of aqueous flow, but one which is subject to considerable variation and error, is the appearance time of fluorescein in the anterior chamber. More extensive investigations of this and two other fluorescent dyes and their appearance in the aqueous humor of rabbit eyes after intravenous administration are reported.[99] At higher doses the appearance time for each of these dyes becomes reasonably constant and similar average times are obtained for all three substances. This suggests flow rather than diffusion alone as the determining factor in the appearance time. However, the nature of this "flow factor" may be not secretion from the posterior chamber but merely temperature-induced convection currents in the anterior chamber. Furthermore, in the hands of this investigator[99] no alterations in appearance time of any of the dyes in rabbit eyes follow the administration of acetazolamide, in spite of adequate reductions in intraocular pressure. Unfortunately these acetazolamide experiments are complicated by the application of a topical anesthetic and a tonometer to the eye. Such procedures may permit fluorescein to enter the anterior chamber more rapidly because of the increase in permeability of iris vessels. This would tend to offset the delay in appearance time seen in the undisturbed eye after acetazolamide administration and may reconcile the discrepancies in part. These experiments need further study with particular attention to the importance of convection currents and altered permeability in the anterior chamber.

The literature for the past few years has a large number of articles related to the effects of various conditions, procedures, and drugs on the "blood-aqueous barrier" as measured by the appearance of fluorescein in the anterior chamber of animal and human eyes.[17,147,479] As emphasized, the fluorescein appearance time as a method for measuring flow depends upon constancy of diffusion and permeability factors, as well as of convection currents in the anterior chamber

without spontaneous or induced alterations. These assumptions are apparently valid only under limited circumstances in a single eye. When different animals or patients are compared, however, the variations found make meaningful measurements impossible unless elaborate efforts are made to apply suitable corrections. Furthermore, even under ideal circumstances, the fluorescein appearance time provides only relative values for the given eye and is not an absolute measure of flow.

On the other hand, the fluorescein technique as commonly used probably measures permeability changes for the most part, but one cannot be certain as to the effects of variations in plasma concentrations, protein binding, secretory activity, and convection currents on the curves obtained. As with other experiments involving only anterior chamber concentrations, the results are difficult to interpret but should stimulate reevaluation by tonographic and turnover methods. Thus intravenous injections of atropine, pilocarpine, or epinephrine hasten the appearance of fluorescein in the rabbit anterior chamber.[870] The rate of penetration of fluorescein in animal eyes is also increased by anticoagulants,[188] convulsions,[204,586,587] hypoglycemia,[198] anaphylactic shock,[166] and acetylcholine but is decreased by oscillation[874] and Irgapyrine.[166]

In human eyes the fluorescein penetration rate is not altered in chronic simple glaucoma, but it is considerably increased in secondary and angle-closure glaucomas.[875] However, some observers report increased permeability in all glaucomas[526,584] and, in fact, claim alterations in capillary permeability other than in the eye. Increased permeability in human eyes is also noted following fever therapy, anesthesia, menstruation, pregnancy, and in various traumatic and inflammatory conditions of the eye.[755] Penetration of fluorescein is said to be more rapid after miotic or histamine administration but to be delayed by epinephrine, antihistamines, cortisone, calcium, rutin, and vitamins of the B complex.

Besides the permeability of the animal eye to fluorescein, the entrance of various other substances has been studied. These include the penetration of electrolytes,[199,348] oxygen,[347] radioactive iodine,[633,730,809] tritium,[270,271] radioactive phosphorus,[731,878,879,880] glucose, serum proteins,[206,337] ascorbate,[41] tetracycline (Achromycin),[234] and other antibiotics.[525] In addition, the influences of various disease processes, hormones,[288,788] vitamins, surgical procedures,[208,209,662,730] and drugs on the rate of appearance of some of these substances in the anterior chamber are reported.

The nature of the vitreous, its formation, composition, alterations, and the possible role it plays in maintaining intraocular pressure, continues to receive attention but still remains a largely unexplored area.[51,66,168,342,354,355,396,719-721,822,823] Values for vitreous bicarbonate and ascorbate fall between the posterior chamber and plasma concentrations.† [193,325] The turnover rates of ascorbate, bicarbonate, thiocyanate, iodides, various sugars, phosphate, sodium, and other substances in the vitreous provide a beginning to the study of the complexities of the dynamics of this important part of the eye.[192,268,322,546,730] Unfortunately, very few of these studies provide simultaneous data on posterior chamber, anterior chamber, and plasma values.

The confirmation of the finding of β-glucuronidase in the ciliary body again leads to speculation as to its possible function in the formation of vitreous and aqueous humors.[87,161,445,785] Although there is evidence to suggest that hyaluronic acid is not secreted by the ciliary body, but rather is found in higher concentrations closer to the retina,[51,720] it is still attractive to speculate that the ciliary body may play some role in the synthesis or breakdown of hyaluronic acid. The recent demonstration of in vitro synthesis of hyaluronic acid by cell-free extracts of the Rous chicken sarcoma and by tissue slices of human synovia pro-

† Shrewsbury, R.; Constant, M. A., and Becker, B.: Unpublished data, 1955.

vide an ingenious approach to this problem.[291,877] Experiments designed to study possible in vitro synthesis of hyaluronic acid by ciliary processes might prove most revealing. The possible relationship of such a synthesis to the transport of electrolytes and water has not been fully exploited. The binding of cations by acid mucopolysaccharides [236] and the enormous potential osmotic effects associated with changes in the state of polymerization of such large molecules present attractive possibilities.

B. Alterations in Rate of Aqueous Formation.—1. Spontaneous Variations and Neurogenic Control of Intraocular Pressure: Reasonable evidence is available that the diurnal fluctuations in intraocular pressure are associated with variations in secretory activity of the ciliary body.‡ [314,519,550,843] In glaucomatous eyes with impaired outflow facility small alterations in secretion can produce larger fluctuations in intraocular pressure than in normal eyes. This difference proves of considerable value in the early diagnosis of glaucoma.[383,428,496,518,519,539,549,550,599,746,790] Some observers believe that the diurnal curve also permits an evaluation of the prognosis and the status of medical control of the glaucoma.[332,333,338,790]

The stimulus and mechanism for diurnal variations in secretory, endocrine, and other functions are matters of much speculation. It is likely that such cyclic variations stem directly or indirectly from mechanisms that are subject to central control in the organism.[746] Speculations as to the nature of diurnal fluctuations in secretion of aqueous humor usually incriminate cerebral and direct neurogenic or neurovascular control of the activity of the ciliary body. Intermediate areas such as the diencephalon and autonomic nervous system or direct or indirect hormonal and metabolic effects also receive consideration. Thus, the control of secretion of aqueous humor provides one common meeting ground for the so-called "mechanical" and "neurovascular" schools of thought.

‡ Becker, B.: Unpublished data, 1955.

As described above, nerve endings are found in the chamber angle,[372,373,838] and thus the facility of aqueous outflow may also be controlled centrally as well as by reflex. However, the presence and nature of such regulation is not yet established. Furthermore, scleral rigidity may present spontaneous or neurogenic-induced fluctuations and may necessitate a reevaluation of recorded diurnal curves based on Schiøtz scale readings.[519] On the other hand, there is somewhat better evidence that secretory processes are controlled centrally, but with suitable modifications by local reflexes, vascular alterations, and enzymatic and metabolic activity of the ciliary body. It seems appropriate, therefore, to consider neurogenic control of intraocular pressure under the heading of alterations in aqueous formation. It is realized that this convenient classification may well require modification.

Alterations of intraocular pressure following stimuli applied in the region of the diencephalon have received additional and more intensive study recently.[294,834,835,836] The complex vascular and neurogenic systemic and ocular changes which follow stimulation in the posterior ventral hypothalamus of the cat have been elucidated carefully. Here an acute rise in intraocular pressure coincides with an increase in blood pressure. All evidence points to an increased intraocular blood flow as the cause of the elevation of intraocular pressure. Possible roles of extraocular muscles or smooth muscle in the orbit are ruled out by the effects of suitable local denervations or blocking agents. Systemic adrenergic blocking agents, such as tolazoline (Priscoline) are effective in abolishing both ocular and blood pressure rises, but cholinergic blockade by atropine proves ineffective. Mechanisms involved in stimulation of other diencephalic areas await similar study.

Punctures of the midbrain increase or decrease intraocular pressure, depending on the site of puncture.[7] Variations of intraocular pressure are also noted with lesions or stimulation of the cerebral cortex.[849,865]

Furthermore, intraocular pressure in the dog may be altered by conditioned reflexes.[627]

Further details of the morphology of the ciliary ganglion with its sympathetic, parasympathetic, and sensory fibers are reported.[460] There is need for more intense study of the physiologic roles and functional aspects of this innervation center for the eye. Such studies are particularly timely in association with current renewed interest in various reflex alterations in aqueous humor dynamics. In rabbits, as well as in patients, the consensual fall in intraocular pressure in the contralateral eye during tonography appears to be dependent upon a decreased secretion of aqueous in that eye.[641] It is of considerable interest that this reaction can be abolished by the systemic administration of atropine to rabbits or ganglionic blocking agents such as pentolinium to patients.[680] Some reflexes can be blocked as well by the retrobulbar injection of procaine in the homolateral eye.[651] It should be noted, however, that all three of these measures (systemic atropine in rabbits, pentolinium in patients, and retrobulbar procaine) decrease the rate of aqueous flow in the first eye. This would mask differences between the two eyes and fail to reveal the reflex changes in the contralateral eye.

The parasympathetic fibers in the seventh nerve appear to have little effect on ocular blood flow or intraocular pressure, since stimulation of this nerve intracranially fails to alter intraocular pressure in the monkey.[321] In fact, there is little evidence that the parasympathetic has much direct effect on intraocular pressure.[320] Stimulation of the cervical sympathetic, on the other hand, produces a fall in intraocular pressure associated with vasoconstriction.[319]

Stimulation of the fifth nerve in rabbits induces a rise in intraocular pressure, but there are differences of opinion as to whether this is a central or an antidromic effect.[7,622,623] The latter view appears more reasonable, since the hypertension is more prominent in the homolateral than in the contralateral eye, is associated with ocular vasodilatation and increased ocular blood flow, and is abolished by section of the fifth nerve. Fifth nerve stimulation may well play a role in the rise in intraocular pressure that follows trauma to eyes of patients or experimental animals.

The clinical significance of neurogenic control of intraocular pressure has occupied a number of investigators over a period of many years. There is no question that stimuli from the eye can affect the central nervous system and its neurovegetative and endocrine functions.[709] There is also little doubt that intraocular pressure is subject to central nervous system control, but the role of such regulation and its disturbances in the pathogenesis of glaucoma remains speculative.

Elevation of intraocular pressure associated with pituitary tumors and acromegaly is described.[7,26,645] Postencephalitic Parkinsonism may be associated with depressions of intraocular pressure, particularly when degenerative changes in the diencephalic region are evident.[127,128] On the other hand, transient rises in intraocular pressure are reported to occur in viral encephalitis with diencephalic involvement.[452] Furthermore, various evidences of general or specific diencephalic dysfunctions and vegetative lability are proposed repeatedly as major factors in clinical glaucoma.[124,125,140,160,187,214,507,594,631,646,649,709,710,811,821] However, there are a number of reports denying such differences in neurovegetative function.[598,811,813]

Psychogenic and cerebral factors in the glaucomatous disorders have been emphasized. Many observers believe them to be a contributing factor in the angle-closure glaucomas,[702,746] and some observers feel that they play a major causative role in all glaucomas.[346,395,708,873] Alterations in intraocular pressure are described following transfrontal lobotomy, and glaucoma patients are reported to demonstrate cerebral atrophy by pneumonencephalography.[155-159] The pathway to the eye is postulated to be neurogenic, neurovascular, or via hormones se-

creted into the circulation or into the spinal fluid.[48,64,115,116,139,278,535,537,576,594,711,712,789,810]

The neurogenic approach to the pathogenesis of glaucoma has resulted in a variety of therapeutic attempts. Some of these have proved reasonably successful in the hands of authors describing them. They include the administration of bromides, barbiturates, chlorpromazine, rauwolfia alkaloids, meprobamate, and ganglionic blocking agents in addition to the peripheral miotic therapy.[212,282,310,413,671,799,800] Some authors advocate such adjuvants as psychotherapy, sleep therapy, hypothalamic irradiation, hot baths, etc.[123,698,828] It is a common experience to find spontaneous decreases in intraocular pressure in glaucomatous eyes on hospitalization of the patient without any alteration in medication.§ [597,746]

Closely related to central mechanisms in the pathogenesis of glaucoma is the concept of glaucoma as a systemic rather than just an ocular disease. This has also led to rather extensive investigations attempting to find systemic alterations in blood chemistry, blood coagulation, capillary and nerve function, etc.[6,65,200,279,377,665,733] On the whole, these efforts do not prove very revealing or conclusive.

It is clear that, in addition to the central mechanisms for the control of secretory rate, the functional capacity of the ciliary body limits the ultimate amount of aqueous secreted into the eye per minute. There is suggestive evidence that hypersecretion of aqueous and the so-called hypersecretion glaucoma may originate from central impulses.[89] However, the group of low-tension glaucomas, in which hyposecretion prevents pressure elevations in spite of impaired outflow, needs further study as to mechanism.[635] Certainly in some advanced glaucomas and in elderly persons there is sufficient atrophy of the ciliary body, which can be demonstrated histologically, to account for an inability of the ciliary body to secrete normal amounts of aqueous. However, there are other instances of very early glaucoma in young persons, with markedly depressed outflow facility, whose intraocular pressure remains normal for long periods. In fact, over 50% of eyes with proven glaucoma subjected to tonometry present a reading within normal limits in spite of cessation of all therapy. A similar state of hyposecretion often follows various surgical procedures on the eye. The local mechanisms or centrally innervated processes involved in the spontaneous suppression of aqueous secretion are not resolved. Interestingly enough, the phenomenon of hyposecretion of aqueous humor is also observed in hereditary glaucoma in rabbits.‖ This is obviously a fruitful field for basic research into the nature and pathogenesis of glaucoma.

A progressive decline of the rate of aqueous secretion with age appears to explain the tonographic data obtained on normal eyes.¶ However, the expected degree of hypotony in elderly persons is not always seen, because of a decrease in outflow facility with age. Ocular hypotension as well as hyposecretion is described in association with myotonic dystrophy [455] and is a common concomitant of pernicious anemia.# Hypotony is also a frequent finding in eyes with retinal detachments, offering opportunities for speculation as to cause and effect.[218] As with most instances of hypotony, these examples appear to represent secretory failure. However, further evaluation of possible alterations in scleral rigidity are needed.

Finally, it is clear that not all centrally innervated and other alterations in intraocular pressure can be resolved into changes in outflow facility or aqueous secretion. For example, it is known that convulsive shock produces an immediate rise in intraocular pressure [586] and that this can be duplicated by the sustained contraction in extraocular muscles induced by succinylcholine.[367,368,497,520] Likewise, sudden alterations in blood

§ Becker, B.: Unpublished data, 1956.

‖ Constant, M. A., and Becker, B.: Unpublished data, 1955.

¶ Becker, B.: Unpublished data, 1956.

Naquin, H.: Personal communication to the author, 1952.

pressure (e. g., the pulse pressure) and ocular blood volume are reflected in the intraocular pressure.

2. Carbonic Anhydrase Inhibition and Aqueous Flow: Clinical and experimental interest in carbonic anhydrase inhibitors continues unabated. In fact, there are as many references to the clinical use of these agents in ophthalmology during the past year as in all preceding years. However, most clinical reports are largely confirmatory of previous publications as to indications and usage. Increasing interest is apparent in the use and the side-effects of acetazolamide administration for extensive periods of time. Several studies are in progress designed to develop and explore the potentialities of newer carbonic anhydrase inhibitors which might prove more effective and induce less side-effects. In the laboratory carbonic anhydrase inhibition is a routine tool for the study of the effects of partial secretory suppression on the chemistry and dynamics of the aqueous humor. Most of the areas of controversy about the mechanism of action of acetazolamide are largely resolved. However, the intimate details of the mode of action of this drug on the ciliary processes must await increased knowledge of the true nature and mechanism of the secretion of aqueous. This important question continues to fascinate research workers and remains a subject of active investigation in several laboratories. It appears likely that the ability to alter the secretory process will hasten the resolution of its complexities.

(*a*) Experimental studies on acetazolamide. In the rabbit, guinea pig,[79] and dog [235] there is an excess of bicarbonate, a deficit of chloride, and a higher pH in the aqueous humor as compared with plasma values. Furthermore, it is possible to obtain posterior chamber samples in the guinea pig and to demonstrate even larger excesses of bicarbonate and deficits of chloride than in the anterior chamber. As in the rabbit eye, all of these values approach closer to the plasma concentrations after partial suppression of secretion by acetazolamide. In the guinea pig alterations in bicarbonate concentration induced by acetazolamide are consistent with an average decrease in the ratio of the flow to the diffusion constant of 58%.[79] This agrees well with the findings in other species.

The over-all agreement on the effects of acetazolamide among several workers in the field of aqueous humor dynamics is exemplified by the conclusions reached at an informal meeting held in Boston in February, 1957. The areas of agreement for acetazolamide effects on rabbit eyes include a lowering of intraocular pressure, a decrease in aqueous humor pH and bicarbonate excess, an increase in ascorbate concentration of the aqueous humor, and a decrease in the rate of secretion of aqueous. Furthermore, it was agreed by various participants in this discussion that acetazolamide lowers intraocular pressure even in the acidotic or nephrectomized animal. Thus, its effects on the eye take place in the absence of the renal action and are likely to be a direct or indirect effect upon the ciliary processes. The area of disagreement is confined to the transient versus continuous action of repeated acetazolamide administration on the rate of secretion of aqueous by the rabbit. The point at issue revolves about whether the restoration of intraocular pressure in some rabbits on continued acetazolamide administration results from a phenomenon of escape from the suppressive effect of acetazolamide on secretory rate [464] or from a compensatory decrease in outflow facility, which restores intraocular pressure in spite of the decreased rate of secretion.[69,82,852] Differences in technique used by investigators may account in part for the variations in results obtained.[74,422,463] Additional data, especially with reference to the chemistries of the posterior chamber aqueous, may help to resolve these questions. In the human eye, particularly in the therapy of glaucoma, there can be little doubt that acetazolamide continues to suppress secretion of aqueous and that true resistance to this effect is exceedingly rare.

During the past year the effects of acetazolamide on the bicarbonate and lactate concentrations in the postior and anterior chamber aqueous humor and plasma have been studied in greater detail and have been found to confirm previous findings.[86,324] The alterations induced by acetazolamide in the sodium and potassium concentrations of the aqueous humor of rabbit eyes have been repeated.[122,255,343,464,483,666] Differences of opinion are expressed as to the small changes induced. Unfortunately, in some experiments the changes in the anterior chamber are measured in the absence of knowledge as to variations induced in plasma concentration. In other investigations the aqueous humor of the anterior chamber is compared with plasma but no determinations are available on the posterior chamber. With substances in the anterior chamber that are so close to plasma in concentration as sodium and potassium, the small anticipated alterations following carbonic anhydrase inhibition would be expected to fall well within the fairly large errors in the flame photometry methods used. This consideration would require a very large number of determinations to obtain data that might prove statistically significant. Furthermore, acetazolamide can induce changes in plasma sodium and potassium levels which further complicate the interpretation of the data. As indicated above, without detailed knowledge of the simultaneous concentrations in the posterior chamber, the data obtained afford little information as to alterations in flow or even as to possible modifications of the secretory concentration of cations.

The increase of ascorbic acid in the aqueous humor of rabbits following acetazolamide administration has been amply verified.[365,464] Similar changes are noted in the dog [235] and in man.[72] The rise noted in the anterior chamber is, of course, slower and not as impressive as that found in the posterior chamber. In the anterior chamber it is partially compensated by the greater opportunity for diffusional loss offered by the slower rate of aqueous flow. The question is raised repeatedly as to how the concentration of a secreted product can be increased by an agent that decreases secretion. This data are even offered as evidence against the currently accepted mode of action of acetazolamide. Such reasoning is based on the assumption that all substances transferred into the eye are secreted by the same mechanism and therefore inhibited to the same degree. If this were so, one would expect to find little alteration in posterior chamber concentrations of the secreted ions and a tendency for greater equilibration with plasma levels of the nonsecreted substances of the posterior chamber and of all constituents in the anterior chamber. In the human pancreas, acetazolamide inhibits the secretion of water and bicarbonate to essentially the same degree (approximately 70%). Thus, no change in bicarbonate concentration in the pancreatic juice is observed in spite of the decreased rate of flow.[401] This is obviously not so for the rabbit, guinea pig, or human eye, for the transfers of water, bicarbonate, chloride, ascorbate, and lactate all appear to be changed in varying amounts by the partial suppression of secretion induced by acetazolamide. In the rabbit eye, the secretion of water appears to be inhibited to a lesser extent than that of bicarbonate, and therefore the excess concentration over plasma levels of bicarbonate decreases in the posterior chamber after acetazolamide. On the other hand, ascorbate secretion is not altered as much as the water of the aqueous humor. Therefore the concentration of ascorbate rises even though the ascorbic acid itself is being secreted in smaller amounts than normal. If one raises the plasma ascorbate to above saturation levels, similar increases in posterior chamber and anterior chamber ascorbate concentrations are still induced by acetazolamide.

The introduction of N-5 substituted derivatives of acetazolamide and related compounds, which have almost no activity as carbonic anhydrase inhibitors, provide excellent control substances for experiments designed to evaluate the effects of the active

compound.[528] In rabbits, the inactive compound related to acetazolamide fails to alter the rate of secretion of aqueous humor as determined by tonography nor does it change the chemical composition of the aqueous humor. Similar control data are available for the partial suppression of secretion of cerebrospinal fluid.[430]

Early studies have appeared on the fate of acetazolamide in the experimental animal.[3] These experiments were carried out with acetazolamide labeled with radioactive sulfur and assume that the label stays with the drug in the active stage in vivo (and that drugs accumulate at their site of action). This fascinating approach to the study of various other drugs has been productive. It is hoped that its extension to acetazolamide administration in various species will provide valuable information as to the site of action of the drug.

In studies of the electron microscopic appearance of the rabbit ciliary epithelium, the systemic administration of acetazolamide produces interesting alterations.[376] Among other changes, these consist of an increase in width of the mitochondria and an enormous increase in the number of cytoplasmic vesicles. The interpretation of these changes is difficult at present. It is interesting to speculate as to whether they are primary effects of carbonic anhydrase inhibition, related to the metabolic disorder it induces directly or indirectly in the ciliary epithelium, or merely secondary to the ocular hypotony induced by the drug. Whether changes in size of mitochondria signify alterations in energy metabolism of the cell remains to be proved by independent methods. Variations in the number of vesicles in the cytoplasm can also be interpreted in variable fashion. Seidel[724] studied "vacuoles" in the ciliary epithelium histologically and believed them to be the secretory product. However, he interpreted the increased number of vacuoles after pilocarpine injections as resulting from an increased rather than a decreased rate of formation of aqueous. It is hoped that electron microscopic techniques can be extended to other species and compared with microenzymatic studies of these and other secretory cells.[508-513,670,770,870]

As indicated above, and contrary to the impression conveyed last year, the aqueous humor of the human eye appears to resemble that of the monkey in its excess of chloride and deficit of bicarbonate as compared with arterial plasma. However, these differences from plasma concentrations are decreased considerably following the administration of acetazolamide.[72] These findings are consistent with the observation that the presence of carbonic anhydrase in a secretory cell does not necessarily imply that bicarbonate is the primary product transported.[430] Thus, carbonic anhydrase is found in the mammalian renal tubule, where it is believed to play a role in bicarbonate reabsorption. However, in the alligator carbonic anhydrase is essential for continued tubular reabsorption of chloride.[182] Similarly, pancreatic secretion is alkaline,[401] but the gastric parietal cells form hydrochloric acid.[632] Yet both of these require carbonic anhydrase for optimum function and are suppressed in part by carbonic anhydrase inhibitors.[795] At present, the simplest assumption explaining the diverse actions of carbonic anhydrase in a variety of active transfer processes is that the enzyme provides bicarbonate buffering capacity directly to the secretory cell or cells. Thus, the cell secreting an acid may itself sustain a rise in pH. This requires buffering much as does the acidosis of the cell secreting an alkaline product. The less adequate buffering capacity introduced by carbonic anhydrase inhibitors results in a partial suppression of the secretory process. The nature of the suppression induced depends upon which link in the process is most susceptible to the altered pH within the cell. There is no reason to believe that this is the same for all cells nor even identical for various secretory products of a single cell. The degree of suppression depends upon the needs of the cell for buffer, the sensitivity of the "weakest link" to pH change, the rate of the uncatalyzed hydration and dehydra-

tion of carbon dioxide, the amount of carbonic anhydrase present in the cell, and the dose of carbonic anhydrase inhibitor and its penetration to the enzyme site. Such a working hypothesis seems to satisfy almost all of the current data on the action of acetazolamide in various cells. It does not deny that effects of such agents in other parts of the body may modify or even play a major role in the alterations of various secretory processes.[573,604]

(*b*) Clinical reports on acetazolamide. The clinical use of acetazolamide for short-term and prolonged therapy of glaucoma has been amply verified, and a large number of publications agree in general with previous data summarized last year.[32,76,130,134,137,138,152,183,197,220,223,232,238,241,258,273,312,317,411,436,505,516,583,595,619,636,690,692,694,793,827,830,851] It is now apparent that acetazolamide is a very useful agent in the therapy of self-limited secondary glaucomas and in the short-term therapy of the acute glaucomas. Its use in long-term therapy of chronic glaucomas has received additional study and appears to be reasonably successful in selected patients. It is important to emphasize the individual differences in response and the need for careful evaluation of dose required for around-the-clock control of intraocular pressure. The main limitations of this form of therapy stem from the side-effects, which account for about two-thirds of the failures. These are severe enough to necessitate discontinuing acetazolamide administration in some 25% to 40% of all patients subjected to such therapy in the various series reported.

Several excellent reviews on the use of acetazolamide have appeared during the past year.[130,131,374] In addition, articles are beginning to appear on the misuse of acetazolamide even in the therapy of the acute glaucomas.[73,162,312] The major abuses stem from the use of such agents to replace surgery or to postpone it unduly in angle-closure glaucoma as well as in some of the secondary glaucomas (e. g., traumatic hyphema). Procrastination in some of these eyes affords the opportunity for unnecessary synechiae formation and permanent damage to outflow channels. In the eye with angle-closure glaucoma, the delay in surgical therapy may necessitate a filtering procedure with its hazards and complications. The simpler and safer cure by iridectomy permits the continued use of normal outflow channels.[162] Another type of misuse of acetazolamide is the inadequacy of amount and frequency of dosage in chronic glaucomas. This results in inadequate around-the-clock tension control in spite of normalization at the time of the office visit. Among the unnecessary and perhaps harmful uses of acetazolamide are its substitution for miotic therapy, its addition to miotic therapy which already controls the glaucoma adequately, its routine use after filtering operations, and its long-term use in unilateral absolute glaucoma. It is clear that with time and experience, the areas of usefulness as well as the contraindications of such agents are becoming defined more clearly. Since the basic defect in most glaucomas is an obstruction to aqueous outflow, secretory suppression remains a useful but palliative adjunct in glaucoma therapy.

Although carbonic anhydrase is present in the retina, lens, vitreous and uveal tract (but absent in the cornea), its inhibition by acetazolamide does not appear to alter the functional status of any of these structures with the exception of the secretion of aqueous humor.[16,50,292,433,440,477,700,869] Thus, after acetazolamide no consistent alterations have been detected in ocular circulation, the appearance or metabolism of the lens, the function of the macula, dark adaptation, flicker-fusion, etc.[24,566] However, another instance of transient myopia is reported associated with a shallowing of the anterior chamber and an increase in intraocular pressure to 40 mm. Hg.[27]

The use of acetazolamide in nonglaucomatous ocular conditions continues to receive enthusiastic support. The results in corneal dystrophy are occasionally striking but more often disappointing.[45,482,765] Good results probably relate to the decreased intraocular

pressure facilitating the deturgescence of the cornea.[22,344] Some recommend the use of acetazolamide in flat anterior chamber and even in routine cataract and glaucoma surgery.[5,46] However, other observers deny that acetazolamide is effective or should be used routinely in such conditions.[706,816,863]

The effects of acetazolamide elsewhere in the body continue to receive attention.[56,221,307,335,336,527,569,570,713,756] There is confusing evidence as to whether it alters carbohydrate metabolism, with some reports indicating that it has a hypoglycemic action and others denying such an effect.[20,326,577,596]

One of the most disturbing side-effects of acetazolamide administration is the occurrence of ureteral colic and calculus formation.* [90,308,625,703] Resembling the finding in rats,[345] there is a remarkable decline in citrate excretion in the urine of normal and glaucomatous persons subjected to even a single dose of acetazolamide.[308,729] The fall in citrate output is much more profound in those patients on continued around-the-clock administration. The decrease in citrate in the urine occurs in the absence of a fall in plasma citrate and without significant alterations in calcium output. The intimate mechanism of this change is not understood. There is abundant evidence in the literature that citrate may play a physiologic role as a chelating agent for calcium.[202,203,228,229,265,429,470,557,722,732] The question naturally arises as to the possibility that the decreased citrate concentration in the urine results in a failure to keep calcium in solution and leads to its precipitation as calculi in the urinary tract.

An additional instance of thrombocytopenia as well as sulfonamide renal lesions has been reported following acetazolamide administration.[102] Although fortunately rare, these serious complications must be appreciated and anticipated by the ophthalmologist using acetazolamide in the therapy of the glaucomas.

(*c*) Other carbonic anhydrase inhibitors. There has been considerable interest during the past few years in the discovery and evaluation of newer carbonic anhydrase inhibitors. These have been developed in order to find more effective agents in the therapy of glaucoma as well as agents which conceivably might cause less side-effects. The 2-propionyl, 2-butyryl, and 2-isobutyryl analogues of acetazolamide (5-acetamido-1,3,4-thiadiazole-2-sulfonamide) are as effective as acetazolamide, with approximately the same dose needed and identical side-effects.† [52] Patients unresponsive to acetazolamide or suffering undue side-effects almost uniformly fail to respond to or to tolerate these closely related compounds. Therefore, these agents have little to offer in the therapy of glaucoma.

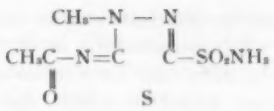
Ethoxzolamide (Cardrase) is an effective carbonic anhydrase inhibitor which lowers intraocular pressure at approximately one-half the dose of acetazolamide (i. e., 125 to 250 mg. every six hours). It is limited to oral use and thus is of less benefit in the acute glaucomas. On chronic administration it has essentially the same side-effects as acetazolamide in spite of the lower milligram dosage. However, some patients note fewer side-effects and somewhat better response to this agent than to acetazolamide; others respond better to acetazolamide and note more side-effects with ethoxzolamide. In such a fashion this new drug appears to have a definite place in the armamentarium of the ophthalmologist.‡

Following a somewhat different approach, Neptazane, a carbonic anhydrase inhibitor, has been developed, which is closely related to acetazolamide in structure

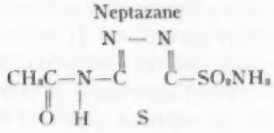
* Leopold, I. H.: Recent Advances in Medical Therapy of Glaucoma (10th Schoenberg Memorial Lecture), read before a meeting of the New York Society of Clinical Ophthalmology, New York, Dec. 10, 1956.

† Becker, B.: Unpublished data, 1955.

‡ Becker, B., and Barnes, C. R.: Unpublished data, 1956.



Neptazane



Acetazolamide

and in vitro has slightly greater activity as a carbonic anhydrase inhibitor. Most important, it penetrates the aqueous humor and spinal fluid more effectively than acetazolamide.[73,76] Interestingly enough, Neptazane (5-acetylimino-4-methyl-Δ^2-1,3,4-thiadiazoline-2-sulfonamide), is found, both in rabbits and in patients, to lower intraocular pressure when administered in doses approximately one-third to one-fifth those of acetazolamide.[74,76] This compound also has three to four times the anticonvulsant activity of acetazolamide in mice [318] but essentially the same diuretic effect. Furthermore, it is excreted more slowly and has a somewhat longer action. At an oral dose level of 100 mg. every eight hours it produces much less diuresis and alterations in circulating electrolytes than does 250 mg. of acetazolamide. As with acetazolamide, there is considerable individual variation in dose required to control the glaucoma, and this is best adjusted on an individual basis during a period of hospitalization. Of great practical importance is the finding that, except for drowsiness and lethargy, most patients note very little if any side-effects from this agent. Alterations in appetite and paresthesias are less common or much less severe even when the drug is used in some patients who could not tolerate acetazolamide because of these complaints. Furthermore, no instances of ureteral colic have been noted to date, and the administration of 100 mg. of Neptazane alters citrate concentration in the urine very little. The drug is available only as an oral preparation at the present time and so receives less attention in the acute glaucomas. However, when used in acute angle-closure or secondary glaucomas it produces as dramatic falls in intraocular pressure as does acetazolamide but not as promptly. The principal applications of this agent at present are in the treatment of those patients with chronic glaucoma who cannot tolerate the side-effects of acetazolamide. Used in this fashion for the past 18 months, it is proving as effective as acetazolamide in most patients, somewhat less adequate than acetazolamide in several, and a better ocular hypotensive agent in a few instances. In all patients it is much better tolerated, however.

In experimental studies in rabbits, Neptazane induces pressure and flow changes similar to those following acetazolamide as measured both tonographically and by alterations in aqueous humor chemistries. However, these can be accomplished with Neptazane at approximately one-fourth the dose.

Chlorothiazide has been introduced as a potent in vitro carbonic anhydrase inhibitor. It has received extensive study as a diuretic agent and has proved to be an agent increasing the urinary excretion of chloride as well as sodium.[250,691] Although the compound was described originally as about 30 times as potent a carbonic anhydrase inhibitor as acetazolamide in vitro,[47,106] it was found to have surprisingly little or no effect on intraocular pressure, aqueous secretion, or chemical composition of the aqueous humor in rabbits.§ Subsequently it has become apparent that this diuretic agent is little more effective as a carbonic anhydrase inhibitor than sulfanilamide. Thus, the lack of action on the eyes of rabbits is explained satisfactorily. Similar independent studies on patient populations reveal that this agent is ineffective in lowering intraocular pressure.‖

§ Becker, B., and Constant, M. A.: Unpublished data, 1957.

‖ Leopold, I. H.: Recent Advances in Medical Therapy of Glaucoma (10th Schoenberg Memorial Lecture), read before a meeting of the New York Society of Clinical Ophthalmology, New York, Dec. 10, 1956.

Another potent agent, Dichlorphenamide, has much the same effects as does acetazolamide on intraocular pressure and aqueous humor composition in rabbits and lowers intraocular pressure in glaucomatous patients. It can be administered in doses approximately one-fifth to one-third those of acetazolamide. Unfortunately, side-effects even at this dose level are essentially those of acetazolamide and in many patients are somewhat more severe (vomiting, dizziness).

3. Other Pharmacologic Agents That Induce Alterations in Rate of Secretion of Aqueous: (*a*) Vasopressin. Continued experiences with the antidiuretic hormone of the pituitary indicate that it is of limited value in the therapy of glaucoma because of the rapid appearance of true resistance. It still finds use as an additional factor in the emergency treatment of the acute glaucomas. The mechanism of action of this drug requires further elucidation. The failure to detect alterations in aqueous humor chemistries poses entertaining questions. Even the reported tonometric and tonographic data may require revision and correction for scleral rigidity alterations.[80]

(*b*) Sympathomimetic drugs. A number of additional studies confirm the long-established hypotensive action on glaucomatous eyes of topically applied epinephrine and related compounds.[76,120,283,606,658,850] Furthermore, those related agents without vasoconstrictor activity, such as isoproterenol (Isuprel), are also effective in lowering intraocular pressure in both normal and glaucomatous eyes.[475,850,858] However, hydroxyamphetamine (Paredrine), ephedrine, Adrenalone, and *d*-epinephrine have little effect on intraocular pressure.[441,572] Repeated tonographic tracings confirm the impression that the active agents in this group decrease the secretion of aqueous.[76,274,275,850] Isoproterenol is well tolerated in 0.5% solution but produces local irritation at a 1% concentration. Although a 4% ointment is effective, palpitation and tachycardia limit its use.[858] It is a vasodilator and does not dilate the pupil.

Epinephrine bitartrate may be made up in a 4.5% solution containing an antioxidant, such as bisulfite, and used topically once a day. When added to miotic therapy this agent is particularly useful in chronic simple and secondary glaucomas. If it is to be used at all in angle-closure glaucomas, care must be taken to avoid mydriasis. It is difficult to understand the mode of action of this drug, and it is particularly frustrating when certain patients do not respond regularly or reliably to the drug, whereas others respond dramatically with profound pressure falls. It is hoped that with additional study its mode of action will be elucidated and by increased understanding the drug can be made more uniformly effective. Of considerable significance is the finding that in many glaucomatous eyes a greater fall in intraocular pressure can be obtained by the combined use of epinephrine and acetazolamide than that induced by either agent alone. This provides additional opportunities for maintaining pressure control and avoiding surgery in chronic simple glaucoma. It also offers additional insight and speculation as to the mode of action of these agents on the process of secretion of aqueous humor.

(*c*) Adrenolytic agents. These drugs have received little study during the past year. It may well be, however, that this is the mode of action of some of the ganglionic blocking and centrally acting drugs. Dihydroergotamine is reported again as a useful agent for lowering intraocular pressure in some acute glaucomas. It is only effective when given parenterally, however.[728]

(*d*) Ganglionic blocking agents. Additional reports have appeared on the transient fall in intraocular pressure that follows systemic hexamethonium.[117] The systemic administration of pentolinium to normal subjects results in small decreases in intraocular pressure and remarkable flattening of tonographic tracings. These findings are interpreted as profound suppressions of the rate of aqueous flow.[680] Recently differences have been noted between the response of glaucomatous and normal eyes.[681] In glau-

coma the tonographic tracings show little further flattening. Thus calculated flow rates are altered much less than in normal eyes. These findings need confirmation and additional study. It would be of considerable interest to learn if there are alterations in scleral rigidity induced by such agents. An induced decrease in scleral rigidity in normal eyes could well account for the tonographic and tonometric data without any alteration in aqueous humor dynamics. In other studies, this and other ganglionic blocking agents are reported to have very little if any effect on intraocular pressure in normal human and animal eyes, but tonographic data are not included.[114,212,530]

(*e*) Agents that act on the central nervous system. Additional studies on chlorpromazine confirm its ability to lower intraocular pressure in rabbit eyes.[174,212] There are conflicting reports as to its action in glaucomatous eyes.[276,310,671] One of the outstanding problems about the pressure-lowering effect of this drug on rabbit eyes is the fact that no alterations are detected in the chemistry of the aqueous humor when the two eyes of an individual rabbit are compared, one eye tested before and the other after the administration of chlorpromazine.[174,212] The question naturally arises as to whether one is altering scleral rigidity or other factors in such fashion as to give false tonometric and tonographic readings. The application of an applanation tonometer to this problem ought to clarify the data. Other tranquilizing agents, such as the rauwolfia derivatives and meprobamate, produce variable effects.[282,413] There are reports of these agents lowering intraocular pressure in animals and human eyes, but others fail to find such changes.

(*f*) Retrobulbar anesthesia. The retrobulbar injection of procaine and epinephrine is noted again to lower intraocular pressure.[163] In addition, the intravenous administration of procaine is said to be a means of lowering intraocular pressure in acute and chronic glaucoma.[43]

(*g*) Osmotic factors. The use of intravenous urea to lower intraocular pressure has received additional study in monkeys.[141, 266] In doses of 5 cc. per kilogram in a 30% solution it proves to be a very effective osmotic agent and produces greater changes in tonometer scale readings in the monkey than does the administration of dextrose, sucrose, or acetazolamide. No reports are available on the use of this agent in treating patients with acute glaucoma, but it appears to have excellent potentialities.

(*h*) Calcium phosphorylcholine chloride. A report reviewed last year indicates that local application of calcium phosphorylcholine produces a rise in intraocular pressure in rabbit and human eyes. This has been confirmed in another clinic,[118] but other observers point out that this is a vasodilating effect of the calcium chloride contained in the compound and may not be related to an action of phosphorylcholine.[312]

(*i*) Other agents. In patients with glaucoma, a rise of intraocular pressure is said to occur after retrobulbar or intramuscular injections of hydralazine (Apresoline).[224] The increase in intraocular pressure is associated with, and probably results from, hyperemia of ocular vessels. A similar rise in intraocular pressure associated with hyperemia is observed following subconjunctival tolazoline. Tonographic data are consistent with the elevation in intraocular pressure resulting from an increased rate of secretion of aqueous.[774,777] This use of tolazoline is proposed as a provocative test for glaucoma.[186,485,488]

Severe acidosis induced by ammonium chloride administration lowers intraocular pressure in the rabbit eye by means of a partial suppression of aqueous secretion.[464] This provides additional confirmation of the suggestion that excessive acidosis can influence the ciliary epithelium and partially inhibit its ability to secrete aqueous humor. Interestingly enough, as in the case of acetazolamide, the administration of ammonium chloride delays the appearance time of fluorescein and results in a rise in aqueous humor ascorbate concentration. The administration of acetazolamide potentiates these effects.[76]

Attempts have been made to learn whether the postulated effect of scurvy on secretion of the aqueous in the guinea pig eye could be verified.[269,717] By perfusion experiments and studies of the alterations in aqueous humor chemistries, the best evidence to date is that scurvy or the administration of vitamin C produces very little change in aqueous secretion or in the concentration of bicarbonate,[79] sodium, or chloride [661] in the aqueous humor. These findings confirm *p*-aminohippurate measurements which reveal no alteration in the calculated rate of aqueous secretion in the guinea pig caused by scurvy or vitamin C administration.[57]

Various traumatic procedures, such as the administration of hydrochloric acid to the eye, exposing the eye to moderate doses of x-radiation,[83] or the systemic administration of iodoacetate,[169] all tend to reduce the rate of aqueous secretion in the rabbit eye as measured by tonography. In all instances this is associated with changes in the permeability of blood vessels. The inflammatory process may alter aqueous formation because the secretory process has to pump against a leaky barrier. Following hydrochloric acid corneal burns, the aqueous ascorbate concentration falls and the steady state *p*-aminohippurate level rises.[13] These findings are consistent with increased permeability. However, the flow rates calculated from careful measurements of *p*-aminohippurate turnover suggest an increase in secretory rate.[13] These discrepancies may stem from low estimates of the aqueous-to-plasma steady-state ratios in these injured eyes or from basic errors or inadequacies of tonographic or *p*-aminohippurate methods.

As reviewed last year, there is evidence that *p*-aminohippuric acid decreases the rate of aqueous secretion in the rabbit eye. Similar observations have been made following the administration of salicylic acid,[718] and more recently reports have appeared on the use of anthranilic acid as an agent for lowering intraocular pressure in chronic simple glaucoma.[392,393]

4. Surgical Means of Changing Rate of Flow: (*a*) Cervical sympathectomy. The reported effects of cervical sympathectomy on rate of secretion of aqueous and on the composition of aqueous confirm earlier findings.[242,662] It is now apparent that removing the superior cervical sympathetic ganglion produces a profound decrease in secretion of aqueous for the first 24 hours. However, this effect is not obtained when the chain is cut in preganglionic fashion in rabbits.[499] In fact, the preganglionic operation provides excellent control studies for tonographic measurements. The alteration in posterior chamber ascorbic acid that accompanies the preganglionic division of the sympathetic is thus dependent upon the alteration in rate of blood flow through the ciliary processes.[662]

(*b*) Cyclodiathermy. Various types of cyclodiathermy and angiodiathermy are described and their beneficial effects in lowering tonometric pressure readings in glaucomatous eyes are reviewed.[1,28,154,277,349,592,603,620,831,854,855] As would be expected, there is a lowering in concentration of ascorbic acid and bicarbonate in the aqueous following cyclodiathermy.[208,209] Such a decreased concentration, however, does not indicate whether one is dealing with a decrease in secretion or an increased diffusion of ascorbic acid and bicarbonate out of the eye. Furthermore, the very interesting observations are made that cyclodiathermy alters the scleral rigidity coefficient and does so in such fashion that its pressure effects may be misjudged.[304] Thus, it may well be that what is interpreted as a normalized intraocular pressure may truly be merely a decrease in scleral rigidity. This important observation needs confirmation urgently, so that the true effects on intraocular pressure of this and related surgical procedures may be elucidated.

(*c*) Other surgical procedures. Rabbit eyes subjected to almost any surgical procedure have prolonged periods of hypotony, and this is associated with increased permeability and decreased secretory rate. Thus,

after iridectomy, radioactive phophorus or fluorescein are found to appear in the anterior chamber more rapidly.[878]

Cyclodialysis performed on a rabbit eye is followed by an immediate interval of ocular hypertension with subsequent cessation of secretion. The hypotony lasts for a prolonged period of time.¶ It is of interest that the prolonged hyposecretory state is associated with histologic evidence of depigmentation and atrophy of the ciliary body in the area of the dialysis.[503] Eyes that are not too severely traumatized do recover reasonably normal secretory activity.

In human eyes there is also evidence for prolonged hyposecretion after cyclodialysis [42,303,881] and also following many other surgical procedures, including cataract extraction.[567] A note of warning should be emphasized with reference to the hypotony resulting from such hyposecretion after glaucoma operations or even cataract surgery. It may provide a false sense of security to the ophthalmologist treating the patient with primary glaucoma or following the aphakic person whose eye has suffered extensive damage to outflow channels.[567] With recovery of secretion the ocular hypertension appears. It is thus of importance to follow these patients closely. Tonography and gonioscopy prove of considerable benefit in detecting and anticipating the rises in intraocular pressure.

The possibilities of introducing Supramid or other plastics in the suprachoroidal space as a means of keeping the cyclodialysis cleft open have been demonstrated and recommended.[768,794]

Choroidal detachments as a complication of antiglaucomatous operations as well as cataract surgery are again analyzed and found to be more frequent than generally appreciated.[451] An excellent review on choroidal detachment appears as an introduction to an experimental attempt at the production of this condition.[151] Apparently both trauma to the sclera and hyposecretion of aqueous are needed for the duplication of this picture in rabbit eyes.

III. Episcleral Venous Pressure (P_v)

The correction for the change in episcleral venous pressure induced by a tonometer resting on the eye during tonography is receiving general acceptance. It is incorporated as an average increase of 1.25 mm. Hg in the tonography tables based upon the 1955 calibration scale.[550] Although it would appear unlikely that the amount of this pressure change would remain constant at all pressures applied to the eye,[304] the differences do not appear to be significant at various tonometer loads.[498]

Further descriptions have been published of the appearance of the aqueous veins, their incidence and location, and their response to mechanical stimuli and to various medications.[12,807,808] In the normal human eye no relation is found between the intraocular pressure and the width of the aqueous veins or the rate of flow in them.[427] Further studies of neoprene casts made by injecting Schlemm's canal in the enucleated eye confirm the relationships in the Schlemm's canal-aqueous vein system in the normal eye. In an eye with acute angle-closure glaucoma and one with secondary glaucoma there was little alteration in the casts.[574] This would be anticipated from the assumed site of pathology in these types of glaucoma.[601]

By taking motion pictures of aqueous veins, a rough estimate is obtained of the rate of flow of "red cell projectiles" in these vessels. From such estimates the potential capacity of the vascular channels appears to be many times larger than the rate of aqueous flow. This is said to suggest that there is very little pressure drop or resistance between Schlemm's canal and the episcleral vessels.[762]

Postmortem injection techniques reveal communications between the anterior chamber and the conjunctival lymphatics in the eyes of newborn infants.[615] Further details of the anatomy of the conjunctival lymphatics in the living human eye are de-

¶ Oglesby, R. B., and Gay, A. J.: Unpublished data, 1956.

scribed.[773] A possible role is suggested for these vessels in the transfer of substances into the anterior chamber following subconjunctival injections.

Details of episcleral, capillary, and venous anatomy and pathology have been further described and studied.[296,399,412] No distinct abnormality appears to characterize the glaucomatous state.

The changes in intraocular pressure that can be induced by postural changes occur in association with similar changes in episcleral venous pressure. Thus, the intraocular pressure and episcleral venous pressure appear to be 1 to 2 mm. higher when the subject is lying flat than when he is sitting up.# [500] An even greater change in intraocular pressure can be demonstrated by comparing the supine position with that standing up.[761]

Attempts to raise episcleral venous pressure as a means of inducing intraocular pressure rises continue to be applied as provocative tests.[225,784] In the hands of most observers these are not very successful in producing more pronounced changes in glaucomatous eyes than in normal ones.

Alterations in episcleral venous pressure have been demonstrated again to be of very little importance in the rise in intraocular pressure found in chronic simple glaucoma.[408] However, additional instances have been reported of elevations of intraocular pressure secondary to obstruction of the superior vena cava.[11] In six patients with mediastinal neoplastic masses the intraocular pressure was normal or somewhat elevated in the upright or semireclining position but rose dramatically in both eyes when the patient was placed in the recumbent position. Interestingly, the elevated intraocular pressures in some of these patients responded to pilocarpine. Unfortunately, no estimates were made of the effects of this agent on episcleral venous pressure or outflow facility in these eyes. As with other intermittent mild or moderate pressure elevations, these eyes presented no evidence of glaucomatous cupping or loss of central visual field.

In a series of hypotonic eyes episcleral venous pressure was found to be within normal limits (i. e., approximately 10 mm. Hg). It is concluded that in such eyes episcleral venous pressure is actually higher than intraocular pressure.[760,763] However, in the absence of scleral rigidity measurements, one cannot be certain that these hypotonic eyes truly had intraocular pressure as low as was indicated. Furthermore, this part of the calibration scale for Schiøtz tonometers is not very accurate.

Reports continue to appear on alterations in systemic venous pressure in glaucoma patients.[119] Interestingly, successful glaucoma surgery is reported to return the disordered rhythm of the systemic venous pressure of the glaucoma patient to within normal limits.[6]

IV. Miscellaneous Glaucoma Topics

A. Visual Fields.—Although glaucomatous eyes are characterized by an increase in intraocular pressure, the definition of glaucoma must include the damage produced to the optic nerve. Thus, cupping and visual field loss continue to provide most important criteria for diagnosis and therapy of the glaucomas.[329,440,806,866]

A well-written and comprehensive textbook and atlas of clinical perimetry has appeared during the last year.[389] In addition to an excellent and lucid review of the anatomy of the visual pathways and the conventional means of measurement, special perimetric techniques are described. Enthusiastic emphasis is placed repeatedly on the greater role of the perimetrist and his rapport with the patient rather than on the equipment used. This textbook is an essential reference in the library of the ophthalmologist.

There is repeated emphasis this year as in past years in the use of perimetry in the diagnosis of glaucoma.[91,280,302,529] It is suggested that all patients over the age of 40 be subjected to routine tangent screen tests.[91] For earlier detection of changes, skiascotometry,[280] the use of gray test ob-

Moses, R. A.: Unpublished data, 1956.

jects [739] or reduced illumination,[21,160,390,529] angioscotometry,[534] flicker fusion,[391,564] ultraviolet fluorescent test objects,[341] and provocative tests (bromides, caffeine, pressure to the eye, emotional upsets, water-drinking) to induce changes in central fields are described.[442,610,801] Unfortunately, field changes in glaucoma may be atypical because of complicating ocular diseases superimposed upon the glaucomatous process.[605] On the other hand, other ocular disease processes as well as retrobulbar lesions may simulate glaucomatous field loss.[217,264,465]

The multiple-pattern test using fluorescent test patterns continues to receive attention and application as a diagnostic test.[669,738] The aphakic patient does poorly in this test, because of the reflection of ultraviolet light from the whole surface of the test card. When the test was applied to a large industrial population, it proved of somewhat limited value because of the high incidence of false-positive results.

One of the most important areas in current thinking about diagnosis and therapy of glaucoma is the vulnerability of the optic nerve head in a given eye to pressure damage.[140,216,264,281,302,678,750] This critical aspect of the glaucomatous disorder probably relates to the blood supply of the optic nerve and other nutritional and metabolic factors, as well as pathologic changes which determine the inherent capacity for a given nerve to withstand intraocular pressure elevations. Intraocular pressure, outflow facility, and secretion of aqueous can be measured and defined statistically. However, the precise pressure that will damage a given eye is the problem faced every day by the ophthalmologist. Unfortunately, at present, it is most often viewed in retrospect. The study of optic nerve metabolism and function has received surprisingly little attention. This neglected area needs most intense study to provide a solid background for a rational approach to the diagnosis and the therapy of chronic glaucoma in the individual eye.

An additional stimulus to investigation of optic nerve function in glaucoma is provided by the interesting observation that, even in advanced glaucoma with marked field loss, the injection of *d*-amphetamine results in an enlargement of the visual field.[597] On the other hand, similar results are reported with the use of vasodilating agents.[404] These exciting results need confirmation and elaboration.

B. Glaucoma Detection.—The importance of glaucoma as a cause of blindness continues to receive emphasis as a public health problem.[44,219,237,457,650] The necessity for early diagnosis and consequent improved prognosis has been affirmed repeatedly.[96, 111,167,190,210,227,297,461,478,825,862] In routine tonometric surveys some 5% to 15% of the population over the age of 40 years are picked up as suspects. In various series some 0.8% to 7% of the total tested are diagnosed as having glaucoma on the basis of more extensive studies.[92,110,309,358,447,456, 487-489,614,660,740] Discrepancies among various series result from lack of uniformity of criteria for diagnosis as well as population differences. The higher incidence is reported in older age groups and in those series where elevations of intraocular tension as measured by the Schiøtz tonometer are accepted as glaucoma; the lowest incidence is reported in those series which require evidence of visual field loss associated with increased intraocular pressure as the criteria for glaucoma diagnosis. As indicated above, the intraocular pressure per se can only be evaluated as to normality in statistical terms. For the individual eye, one must have knowledge of the vulnerability of the optic nerve head. To date, this function cannot be readily estimated.

Unfortunately, there are other limitations to attempts at early diagnosis of glaucoma. Problems of lack of uniformity of tonometer construction, calibration, and usage preclude comparison among different studies. Furthermore, variations in scleral rigidity from the assumed average value can lead to the false impression of an elevated intraocular pressure. Even more significantly, glaucomatous eyes with low rigidity may not be

detected in routine tonometric surveys because they present Schiøtz readings within normal limits. The problem becomes still more complex because patients with glaucoma and impaired outflow facility present spontaneous variations in secretory behavior and thus can at times appear with an intraocular pressure within normal limits because of hyposecretion of aqueous humor. In fact, on routine tonometry less than half of a series of patients with untreated established glaucoma and field loss presented an intraocular pressure of 24 mm. Hg or more. For this reason, there is increasing evidence that tonometric surveys conducted with Schiøtz tonometers should select a scale reading of 4 or less with a 5.5 gm. weight for referring the patient for more intensive study. However, this will lead to an excessive number of referrals and the associated emotional trauma. Thus, although tonometry is essential for the detection of glaucoma and may be recommended for use in the offices of general practitioners, it still leaves much to be desired for the recognition of all patients with glaucoma. It also presents a number of limitations in terms of technical and mechanical difficulties as well as of standardization and individual alteration. The development of effective screening methods constitutes one of the most important public health measures facing ophthalmology.[457]

A part of this confusion can be avoided if surveys are conducted with carefully calibrated applanation tonometers.[302] With this instrument the average intraocular pressure for 400 eyes was found to be 15.44± 2.75 mm. Hg.[304] This reading in the sitting position is in excellent agreement with mean values reported for the Schiøtz measurement (16.5 to 17.5 mm. Hg) as interpreted with the 1955 scale.[15,74,340,378,857] It would seem advisable to follow the applanation reading with tonography, ophthalmoscopy, and perimetry on all patients surveyed who present a true intraocular pressure greater than 20 mm. Hg.

A method has been described for detecting elevations of intraocular pressure by subjective changes in the color of an electrically generated phosphene.[378] This subjective method would be useful in mass surveys, but it first needs careful large-scale study and comparison with applanation tonometry and tonography.

C. Glaucoma Records and Pamphlets.—In clinic populations it proves extremely valuable to separate patients with glaucoma from the rest of clinic patients and to establish separate and complete record forms for the charting of histories, progression of fields, and intraocular pressures, as well as provocative tests, tonography, changes in therapy, etc.[93]

In the hands of several ophthalmologists and glaucoma clinics, instruction leaflets for distribution to glaucoma patients have been used with benefit.[97,334,488] In general, these include a description in lay terms of the nature of glaucoma; the concept of pressure damage to the optic nerve; the mechanism of action of such therapy as miotics, acetazolamide, and surgery, and the necessity for continued control and frequent follow-up. Such pamphlets not only establish better rapport with the patient but lead to more reliable therapy and more regular attendance.

D. Nonglaucomatous Aspects of Intraocular Pressure.—Further experimental evidence appears to confirm the effects of intraocular pressure on in vitro hydration of the cornea.[22] In addition, the cornea which has been hydrated by refrigeration can detergesce more readily at 37 C if intraocular pressure is reduced.[344] This is consistent with the clinical relationship of intraocular pressure to corneal edema, particularly as viewed in patients with early endothelial dystrophy.

A very interesting study has appeared on the role of the intraocular pressure in the developing chick eye. When intraocular pressure is reduced by a vitreous cannula, the growth of the eye is arrested and the cornea and lens fail to increase in size

normally.[180,181] Another study in the chick provokes entertaining speculation. This is the finding that exposure to continuous illumination results in a larger eyeball than does exposure to 12 hours of light per day.[406] Since this occurs without significant difference in body weight, its mechanism needs elucidation. This project presents many of the problems discussed in this review—the measurement of intraocular pressure and its role in enlargement of the globe, possible secretory and outflow alterations, the effects of ocular and systemic therapy, differences in chemical composition of the aqueous humor, effects upon the optic nerve and visual status, and the nature of the changes induced by the alteration in diurnal light stimuli which result in possible central nervous system reactions as well as neurogenic, neurovascular, endocrine, metabolic, nutritional, and other effects upon the eye.

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News and Comment

SOCIETY NEWS

Société française d'ophthalmologie.—The French Society of Ophthalmology held its 64th yearly meeting in Paris, May 12 through 16, 1957.

There were, as usual, a great number of foreign members, mostly from Europe but some also from the Western Hemisphere.

This year the main paper (Rapport) was on the slit-lamp examination of the vitreous and fundus. It had been written by Archimede Busacca, of São Paulo; Hans Goldmann, of Bern, and Suzanne Schiff-Wertheimer, of Paris.

This is a large book of 382 pages with 141 figures in black and white and 40 beautiful colored plates. (This book is distributed free of charge to all members of the French Society. Nonmembers can obtain it by applying either to the Treasurer of the Society, Dr. J. Charpentier, 28, rue Vignon, Paris IX, or to the publisher, Masson & Cie, 120 boulevard St. Germain, Paris VI. The price of the volume is 8000 francs.)

The book begins with general considerations and with geometric optics by Goldmann. Chapter IV, by Busacca, deals with the anterior vitreous. In Chapter V Goldmann takes up the rest of the vitreous (normal vitreous and detachment of the vitreous). Chapter VI is by Goldmann on the examination of the peripheric fundus; Chapter VII, by Busacca, on the central part of the fundus; Chapter VIII, by Schiff-Wertheimer, on the study of the fundus and vitreous in retinal detachment. Chapter IX, by Schiff-Wertheimer, is a study of cystic edema of the retina and macular holes. Chapter X, by Goldmann, deals with intraocular tumors. Chapter XI, also by Goldmann, deals with the disc, and the last chapter, also by Goldmann, is a description of retinal surgery with the help of the slit-lamp and contact lenses.

This main paper was presented by the three authors on Tuesday, May 14, and this was followed by a long discussion.

On Monday, May 13, the papers were devoted to the cornea. Postic (Novi Sad, Yugoslavia) read a paper on the keratitis of chickenpox. This ran a prolonged course and did not seem to respond to any treatment. Sedan (Marseilles) studied 146 observations of syphilitic interstitial keratitis treated before 1950, without cortisone, and 24 treated since then, with cortisone. He found that recurrences were more frequent with cortisone but of shorter duration. Final vision with cortisone was definitely better than without. Paycha (Montpellier) stressed the value of a careful history in the consideration of corneal diseases. Franceschetti, Chodos, Dieterlé (Geneva), and Forni (Bellinzona) gave the description of a second case of deep filiform dystrophy of the cornea. Bouzas (Athens) reported on a patient who started with a typical case of Eales' disease and after four years has now the usual symptoms of Behcét's disease. He had observed two similar instances and wondered whether there was not a connection between the two diseases. Druault-Toufesco (Tours) thought that the study of the recovery time after a retina is exposed to strong light is of interest in disease of the retina and may enable us to foresee complications such as detachment. Larmande and Margaillan (Algiers) report on a case of Paget's disease with Groenblad-Strandberg syndrome. Huber (Zurich) has used electromyography in the study of myasthenia and paralysis of ocular muscles. Barraquer (Barcelona) and Bailbe (Perpignan) reported favorably on the inclusion of Strampelli's plastic lens in the anterior chamber after cataract extraction.

On Wednesday, May 15, the papers were on retinal circulation. Bailliart (Paris) gave a short paper on physiopathology, and Lobstein (Strasbourg) read one on dynamics of the retinal and cerebral circulation. Vanysek (Brno, Czechoslovakia) read a paper on electroretinogram in vascular disturbances. Stankovic and Plavsic (Belgrade) studied the effect of ganglionic block on the retinal and the general blood pressure in hyperpiesis. Dejean (Montpellier) read

a paper on the disturbances of retinal and vitreal circulation in the embryo and their fibroplastic consequences. Viallefont, Boudet, and Billet (Montpellier) gave a study of retinal blood pressure and ocular tension in coma induced by insulin (Sakel). Jean-Gallois (Paris) claimed that the use of vasodilating drugs, although it had no effect on the course of myopia, could momentarily improve the vision. Baron (Nantes) reported on four cases of temporal arteritis with pathologic examination. Streiff (Lausanne) read a paper on retinal arteritis and severe chronic progressive polyarthritis. These are exceptional. Mawas (Paris) gave a description of the nerve supply of retinal blood vessels. François, Neetens, and Collette (Ghent) have roentgenologically examined thin section (5μ to 100μ) of ocular tissues. The normal retina and optic nerve are quite transparent to x-ray, but any disturbance shows up by absorbing the rays.

Sunday, May 12, was devoted to free papers. Bregeat and co-workers (Paris) reported on the favorable results obtained with radioactive substances placed within the sella. Dubois-Poulsen and Magis (Paris) stated that an enlargement of the blind spot was very often suggestive of a chiasmatic lesion. Lavat (Paris) gave a description of a new method for treating anomalous correspondance with the major amblyoscope. Thiebaut and Matavulj (Strasbourg) reported on three cases of nystagmus retractorius. Pavisic (Zagreb) reported on the use of the ear cartilage for the repair of lid colobomas. Strampelli (Rome) gave a favorable report on the treatment of retinal detachment with a macular hole by the use of ultraviolet rays. Zanen, Wibail, and Meunier (Brussels) reported on the achromatic threshold in congenital dyschromatopsias. Bengisu (Istanbul) reported on three cases of Marfan syndrome.

Thursday, May 16, was also given over to free papers. Rouher (Clermont Ferrand) had observed three children with typical symptoms of reticulosarcoma of the orbit. He abstained from biopsy, and the children have survived up to now six, five, and three years. Algan (Nancy) considers that the heredity of congenital glaucoma is recessive. Hartmann and Saraux (Paris), by injecting 200,000 units of vitamin A, obtained a marked hypotony, which, they believe, is due to inhibition of vitamin C. Legrand, Hervouet, and Lenoir (Nantes) after studying five eyes operated on by iridencleisis consider that best results are obtained when the incision is neither too anterior nor too posterior but exactly at the surgical limbus. Trantas (Athens) has studied the information obtainable in glaucoma by the appearance of the red ring in the angle. Etienne (Lyons) observed a case of glaucoma due to a congenital constriction of the pulmonary artery. Miller, Divert, and Crouzet (Paris) reported on the favorable effect of decamethylene bromide in glaucoma. Mercier (Tours) stressed the fatigue of many normal persons, under normal circumstances, such as television, fluorescent light, observation of radar screens, and high-altitude flying. Abrahamson (Cincinnati) reported favorably on Metimyd and Metroton.

On Tuesday afternoon several surgical films were presented. On Monday and Thursday there were operations and demonstrations in several Paris hospitals.

On Tuesday, May 14, the usual banquet was held, with M. René Onfray presiding, and the next afternoon an excursion was organised to Versailles.

Several other ophthalmological organizations met during the same week: The International Organization Against Trachoma, The Society for Prevention of Blindness, and the Entretiens thérapeutiques.

The 65th meeting of the French Society of Ophthalmology will be held in Paris, May 11 through 15, 1958.

ANNOUNCEMENTS

Eastern Section Meeting, Association for Research in Ophthalmology.—The annual meeting of the Eastern Section of the Association for Research in Ophthalmology will beheld at the National Institutes of Health, Bethesda, Md., Jan. 16, 17, and 18, 1958.

The first part of the meeting will consist of a symposium on electrophysiology of the visual system. It is planned to present a cross section of work in this general area. The second part is reserved for free papers.

The local chairman, Dr. Ludwig von Sallmann, would appreciate receiving abstracts before Nov. 15, 1957, in order to allow for the publication of the program in ophthalmological journals prior to the meeting.

Call for Papers and Exhibits.—The 1958 Meeting of the Section on Ophthalmology will be held in San Francisco, June 23-27, 1958, simultaneously with that of the Association for Research in Ophthalmology.

Any one wishing to present a paper before the Section is urged to communicate with Dr. Harold G. Scheie as soon as possible. A title and abstract of 50 to 150 words must be in his hands by Jan. 1, 1958. Anyone wishing to present a paper before the Association for Research should contact Dr. Lorand V. Johnson as soon as possible. A $250 prize is offered for the best paper presented before the Section at each Scientific Session. Send communications to Harold G. Scheie, Secretary, Section on Ophthalmology, 313 S. 17th St., Philadelphia 3; Lorand V. Johnson, Secretary, Association for Research in Ophthalmology, 10515 Carnegie Ave., Cleveland 6.

Anyone wishing to prepare a scientific exhibit should communicate with Dr. Frank W. Newell as soon as possible. A $250 prize is offered for the best scientific exhibit prepared for the Section on Ophthalmology at each Scientific Session. Write to Frank W. Newell, Representative to Scientific Exhibits, 950 E. 59th St., Chicago 37.

National Council to Combat Blindness.—The Scientific Advisory Committee of the National Council to Combat Blindness, Inc., 41 W. 57th St., New York 19, announces that it is now accepting applications for its 1958-1959 Fight for Sight Grants-in-Aid, Research Fellowships, and Summer (1958) Student Fellowships. In accordance with its program of financing research in ophthalmology and related sciences and encouraging qualified investigators to further research, the Scientific Advisory Committee will consider all applications at its Ninth Annual meeting, scheduled in June, 1958.

The closing date for receipt of completed applications for grants and fellowships has been advanced to March 1, 1958, in order to allow ample time for processing and review. Applications for Summer Student Fellowships will be reviewed in advance of the June meeting. Appropriate forms may be obtained by addressing Secretary, National Council to Combat Blindness, Inc., 41 W. 57th St., New York 19, the Council's new address.

The Scientific Advisory Committee consists of nineteen members: thirteen ophthalmologists, two physiologists, one biochemist, one microbiologist, one psychologist, and one zoologist. The Chairman is Charles A. Perera, M.D., Associate Professor, Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, New York. The other members are James H. Allen, M.D., Tulane University; Bernard Becker, M.D., Washington University; Alson E. Braley, M.D., University of Iowa; Frederick Crescitelli, Ph.D., University of California; Arthur G. DeVoe, M.D., New York University-Bellevue Medical Center; Dan M. Gordon, M.D., New York Hospital, Cornell Medical Center; Charles Haig, Ph.D., New York Medical College; Michael J. Hogan, M.D., University of California; Peter C. Kronfeld, M.D., University of Illinois; Irving H. Leopold, M.D., Wills Eye Hospital; A. E. Maumenee, M.D., Johns Hopkins University; Karl Meyer, M.D., College of Physicians and Surgeons, Columbia University; Stuart Mudd, M.D., University of Pennsylvania; Lorrin A. Riggs, Ph.D., Brown University; Theodore C. Ruch, Ph.D., University of Washington; Samuel L. Saltzman, M.D., New York Medical College, Flower and Fifth Avenue Hospitals; Kenneth C. Swan, M.D., University of Oregon; Phillips Thygeson, M.D., University of California.

The goal of the National Council to Combat Blindness is the alleviation of defective sight and blindness through the financing of grants and fellowships approved by its Scientific Advisory Committee. The 1957-1958 Fight for Sight research allocations amounted to $128,000. These included twenty-four Grants-in-Aid, ten Research Fellowships, and twenty-four Summer Student Fellowships. Awards were made in sixteen states (twenty-eight institutions) and in Canada, Israel, and Japan. Following are the 1957-1958 Fight for Sight awards:

Grants-in-Aid

Investigator	Institution	Project Title	Amount
Adler, Francis H., M.D., and Frayer, William C., M.D. (continuation)	Department of Ophthalmology, Hospital of the University of Pennsylvania	Study of the factors involved in the proliferation of the retinal pigment epithelium in disease	$3500
Balazs, Endre A., M.D. (continuation)	Retina Foundation, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School	Studies of the hyaluronic acid formation in the vitreous body	3700
Ballen, Peter H., M.D.	Department of Surgery, Division of Ophthalmology, State University of New York, College of Medicine at New York City, Brooklyn	Mucous membrane grafts in lye (chemical) burns with reference to method of healing action and vascularization of cornea	2000
Bettman, Jerome W., M.D., and Fellows, Victor, M.D.	Department of Surgery, Division of Ophthalmology, Stanford University Medical School, San Francisco	The effect of pressure, including tonography, on the intraocular blood volume	2750
Breinin, Goodwin M., M.D. (continuation)	Department of Ophthalmology, New York University Post-Graduate Medical School, New York University - Bellevue Medical Center	Electromyography of the extraocular muscles, including stimulation studies and evaluation of drug effects on the action current	2500
Burns, Robert P., M.D.	Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, New York	Tissue culture of generalized cytomegalic inclusion disease virus with electron microscope studies	1000
Byerly, Baxter H., M.D.	North Carolina Memorial Hospital, University of North Carolina School of Medicine	A study of bizarre corneal disease indizenous to American indians in eastern North Carolina	550
Cibis, Paul A., M.D. (continuation)	Department of Ophthalmology, Washington University School of Medicine, St. Louis	Histopathology of the eye with oblique illumination	5600
Drance, Stephen M., M.D.		Purchase of equipment for use by investigator now in Medicine Hat, Alta., Canada, for study in collaboration with Dr. Antoinette Pirie, Nuffield Laboratory, University of Oxford England; project: study of lens epithelium following irradiation	1000
Eliasson, Sven G., M.D.	Department of Internal Medicine, The University of Texas Southwestern Medical School	The role of visual impulses in the control of eye muscle activity	5000
Ellerbrock, V. J., Ph.D. (continuation)	School of Optometry, Ohio State University	Preparation of volume on aids for persons with subnormal vision	500
Garron, Levon K., M.D., and Foerster, Helen Campbell	Francis I. Proctor Foundation for Research in Ophthalmology, University of California Medical School	Special histopathologic study of endogenous uveitis	4400
Gordon, Dan M., M.D. (continuation)	Department of Ophthalmology, New York Hospital,Cornell Medical Center	Application of visual aids in patients with subnormal vision	3675
Green, Harry, Ph.D.	Research Department, Wills Eye Hospital, Philadelphia	Osmotic pressure of intraocular fluids	3500
Green, Harry, Ph.D. (continuation)	Research Department, Wills Eye Hospital, Philadelphia	Intraocular pressure and the bicarbonate ion concentration in animal eyes	5000
Hepner, Ray, M.D.	Department of Pediatrics, University of Missouri School of Medicine	The effects of maternal hyperoxemia on the intrauterine development of the eye	1000
Jacobson, Jerry H., M.D. (continuation)	Division of Electrophysiology, New York Eye and Ear Infirmary	Electrophysiology of the eye	2500
I. C. Michaelson, M.D., and Blumenkranz, Nelly, Ph.D. (continuation)	Department of Ophthalmology, Hadassah University Hospital, Jerusalem, Israel	(a) Mucopolysaccharide content of vitreous humor in normal and abnormal conditions (b) Mucopolysaccharide content of the conjunctival secretion in certain diseases of the conjunctiva	3600
Mitsui, Yukihiko, M.D. (continuation)	Department of Ophthalmology, Kumamoto University Medical School Kumamoto, Japan.	Study of trachoma virus by cultivation and electron microscopy	1200
Pogell, Burton M., Ph.D. (continuation)	Wilmer Ophthalmological Institute, Johns Hopkins University Medical School, Baltimore	Metabolism and turnover of mucopolysaccharides in cornea	4000
Schueler, Fred Warren, Ph.D.	Department of Pharmacology, Tulane University School of Medicine, New Orleans	The effect of hemicholiniums on the cholinergic functions of the eye	1100
Smelzer, George K., Ph.D. (continuation)	Department of Ophthalmology, College of Physicians and Surgeons, Columbia University, New York	The relation of the exophthalmogenic and throtropic pituitary principles	1800
Tsutsui, Jun, M.D. (continuation)	Department of Ophthalmology, Okayama Rosai Hospital, Okayama University, Okayama, Japan	Clinical and virological studies in trachoma	1800
Wolken, Jerome J., Ph.D. (continuation)	Biophysical Research Laboratory Eye and Ear Hospital, University of Pittsburgh Medical School	Photoreceptor structures	2700

Predoctoral and Postdoctoral Research Fellowships

Investigator	Direct Supervisor	Institution	Project Title	Amount
Barishak, Y. Robert, M.D.	Michael J. Hogan, M.D.	Francis I. Proctor Foundation for Research in Ophthalmology, University of California	(a) Implantation of tumor tissue into the anterior chamber of animals (b) Investigations on the tissue culture of intraocular tumors, particularly malignant melanomas	$3600
Bishop, Harding E., B.Sc.	Austin H. Riesen, Ph.D.	Department of Psychology, University of Chicago	Are innately determined connections between retina and brain responsible for vision?	2700
Farkas, T. G., A.B. (continuation)	Normand L. Hoerr, M.D.	Department of Anatomy, Western Reserve University, Cleveland	Role of insulin in the metabolism of the lens	3600
Krishna, Narendra, M.B.B.S.	Irving H. Leopold, M.D.	Department of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine	(a) Influence of drugs on ocular function (b) Attempts to produce diabetic retinopathy in experimental animals	3300
Maurice, David M., Ph.D.	Michael J. Hogan, M.D.	Francis I. Proctor Foundation for Research in Ophthalmology, University of California	Transfer of proteins between blood and intraocular fluids	5000
Modrell, Robert W., B.A., M.A.	Albert M. Potts, M.D.	Department of Surgery, Western Reserve University, Cleveland	Studies on electrophysiology of the eye	2500
Norton, Herman J., Jr., M.D.	Irving H. Leopold, M.D.	Graduate School of Medicine, University of Pennsylvania	Participation in advanced training program for certified ophthalmologists, in research, teaching, and administration techniques	1200
Pratt-Johnson, John A., M.D. (continuation)	J. W. Bettman, M.D.	Department of Ophthalmology, Stanford University Medical School, San Francisco	Corneal transplantation with particular reference to elimination of delayed sensitivity reaction as a result of homotransplantation: metabolism and turnover of polysaccharides in cornea and lens, as well as other chemical and allergic reactions which take place in the recipient's eye	4800

Traveling Fellowships

Investigator	Institution	Purpose	Amount
Haig, Charles, Ph.D.	Department of Physiology, New York Medical College	Under a National Council to Combat Blindness Grant-in-Aid, this investigator conducted a study entitled "Certain Correlates of Structural to Functional Parameters for the Luminence Threshold of the Human Eye"; this traveling fellowship enables him to accept a special invitation from Dr. G. B. B. M. Sutherland to attend a Symposium on visual problems of color; attendance at this Symposium, where colleagues from nine countries will discuss problems in this scientific area, will be of great value to the investigator in the preparation of papers for publication	520
Wolken, Jerome J., Ph.D.	Biophysical Research Laboratory, Eye and Ear Hospital, University of Pittsburgh Medical School	A grantee of the National Council to Combat Blindness for the past 4 years, this Fellowship is enabling him to visit institutions in Italy, Denmark, Sweden, and the British Isles, to consult on the problem on which he is engaged with other experts in the field; project: photoreceptor structures	1500

Summer Fellowships

Investigator	Direct Supervisor	Institution	Project Title	Amount
Alexander, Richard K.	L. Vernon Scott, Sc.D.	Department of Microbiology, University of Oklahoma School of Medicine	Latent herpes simplex infection of the eye	$600
Applebaum, Seymour	Max Chamlin, M.D.	Department of Ophthalmology, Albert Einstein College of Medicine	Problems of electrophysiology and retinal detachment	400
Bard, Leslie A.	Burton H. Pogell, M.D.	Wilmer Ophthalmological Institute, Johns Hopkins University	The role of mucopolysaccharide metabolism in the pathogenesis of diabetic retinopathy	600
Benoit, Richard P.	Alfred Marshak, Ph.D., and Wm. Stone Jr., M.D.	Massachusetts Eye and Ear Infirmary, Marine Biological Laboratory	Radioautographic studies on the problem of chromosome replication in the endothelium of marine animals	600
Berman, Robert W.	Harry A. Feldman, M.D.	Department of Preventive Medicine, State University of New York at Syracuse	Relationship of toxoplasma infections to congenital and acquired chorioretinitis	600
Crawford, Joseph B.	Samuel J. Kimura, M.D.	Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine	Studies on experimental herpes simplex uveitis	600
Dickerson, John W.	Wolfgang A. Lieb, M.D.	Department of Ophthalmology, Medical College of Virginia	The immune response in corneal homo- and hetero-transplants	600
Farr, James H.	Milton Flocks, M.D.	Department of Ophthalmology, Stanford University School of Medicine	The influence of trabeculectomy on the facility of aqueous outflow	600
Giles, Kenneth M.	John E. Harris, Ph.D.	John E. Weeks Memorial Lab., University of Oregon Medical School	The movement of insulin across blood aqueous humour	600
Gondelman, Martin	Joseph Mandelbaum, M.D.	Department of Surgery, Division of Ophthalmology, State University of New York, College of Medicine, Brooklyn	Dark adaptation	400
Jewett, Robert E.	Harold F. Falls, M.D.	Department of Ophthalmology, University Hospital, University of Michigan Medical School	The social, economic, and hereditary aspects of the blind marrying the blind	400
Jones, Helen S., Ph.D.	Alfred Marshak, Ph.D., and Wm. Stone Jr., M.D.	Massachusetts Eye and Ear Infirmary; Marine Biological Laboratories	Investigation of the composition of the aqueous humour of marine teleosts and elasmobranchs in relation to theories of the mode of its formation	600
Keenan, George J.	Earl Fisher, Ph.D.	Department of Ophthalmology, Tulane University School of Medicine	A study of the mechanism by which cellular materials produced by staphylococci are able to produce ocular damage	600
Lieberman, Theodore	R. M. Fusanella, M.D., and Bernard Zuckerman, M.D.	Department of Surgery, Section of Ophthalmology, Yale University School of Medicine	Corneal reactions to iron in foreign bodies	500
Moyers, Thomas G.	L. K. Garron, M.D.	Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine	Electronic microscopic studies on the trabecula meshwork of the human eye	500
Oglesby, Richard B.	Bernard Becker, M.D.	Department of Ophthalmology, Washington University School of Medicine	Uptake of radioactive sulfate by the cornea	600
Reinecke, Robert D.	David G. Cogan, M.D.	Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard University Medical School	Quantitative variations of intraocular pressure due to autonomic innervation	600
Rubin, Herbert S.	Goodwin M. Breinin, M.D.	Department of Ophthalmology, New York University College of Medicine and New York University Post-Graduate Medical School	Electrophysiologic studies in ocular motility	500
Rubin, Walter	Edward W. D. Norton, M.D.	Department of Ophthalmology, Cornell University Medical College	Studies related to the gelling capacities of the vitreous	600
Sabesin, Seymour M.	Ralph Z. Levene, M.D.	Department of Ophthalmology, New York University Post-Graduate Medical School	A study of ocular blood flow in experimental animals	400
Shamblin, James R., Jr.	F. W. Schueler, Ph.D.	Department of Pharmacology, Tulane University School of Medicine, New Orleans	The effect of hemicholiniums on the eye	600
Srebro, Richard	Bernard Becker, M.D.	Department of Ophthalmology, Washington University School of Medicine	Improved methods of electronic tonometry	600
Terry, William D.	Peter H. Ballen, M.D.	Department of Surgery, Division of Ophthalmology, State University of New York College of Medicine, Brooklyn	Mucous membrane grafts in lye (chemical) burns with reference to methods of healing action and vascularization of cornea	600
Wolfe, Richard L.	Ronald Wood, Ph.D.	Wilmer Ophthalmological Institute, Johns Hopkins Hospital	Pathogenesis of ocular diseases: an experimental determination of antibody titers to streptococci in serum from patients with granulomatous uveitis	600

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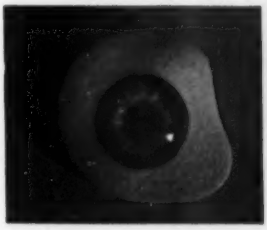

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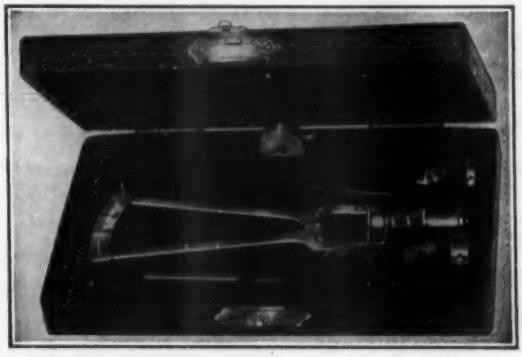

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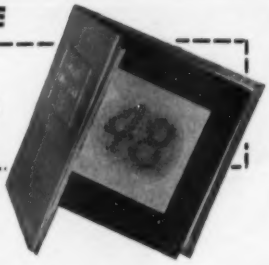

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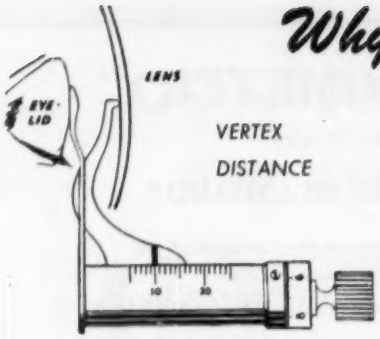

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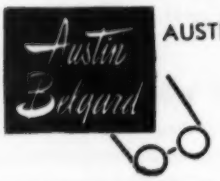

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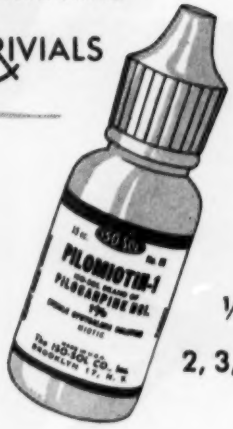

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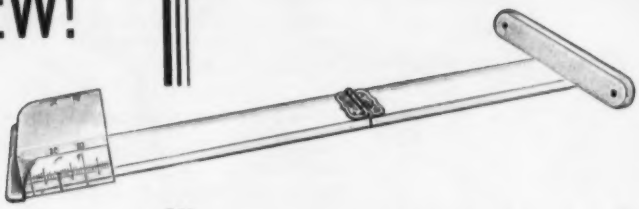

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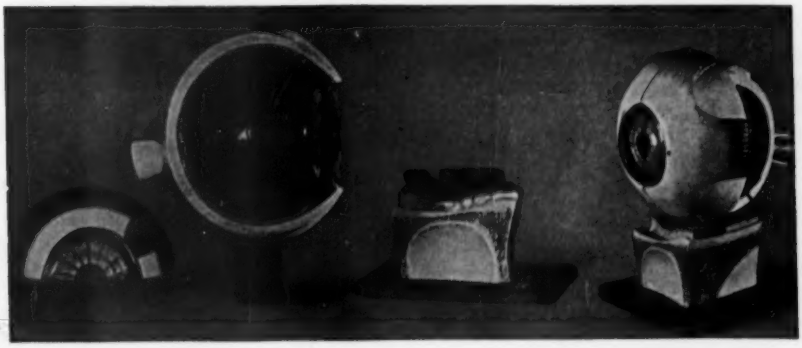

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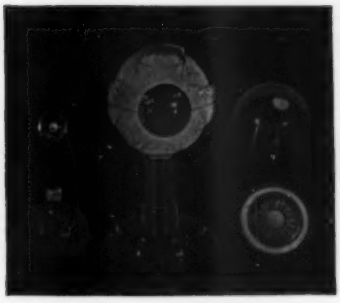

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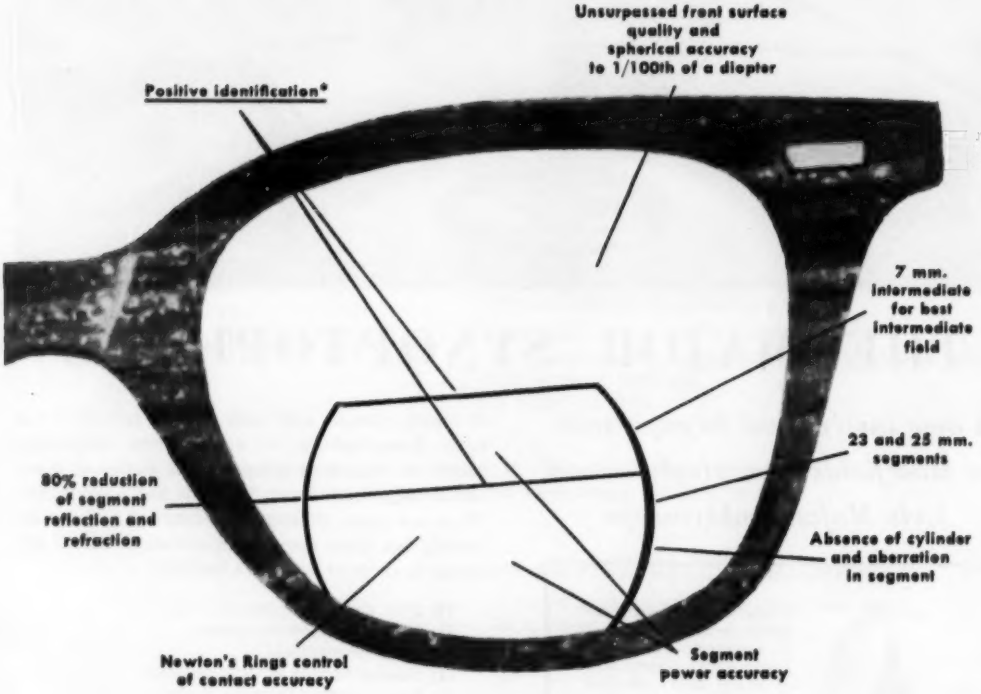
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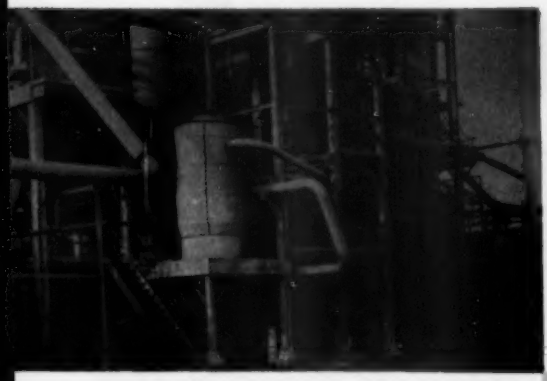

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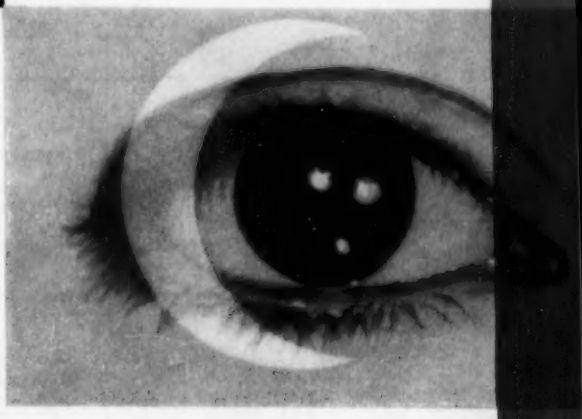

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2. Kuhn, H. S.: Tr. Am. Acad. Ophth. *55*:431, 1951.

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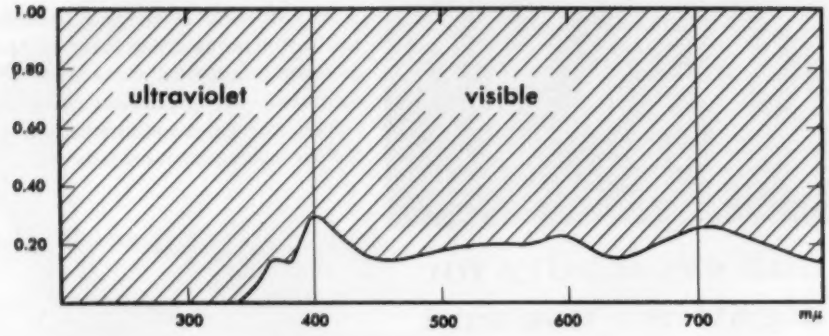

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